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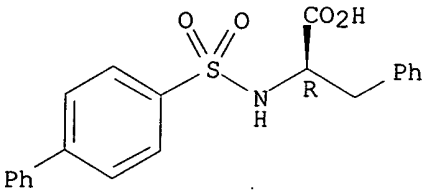
L5 ANSWER 62 OF 62 REGISTRY COPYRIGHT 2002 ACS
RN 193807-58-8 REGISTRY
CN D-Phenylalanine, N-([1,1'-biphenyl]-4-ylsulfonyl)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C21 H19 N O4 S
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Absolute stereochemistry. Rotation (+).




514/562

**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

4 REFERENCES IN FILE CA (1967 TO DATE)
4 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L36 ANSWER 6 OF 9 USPATFULL

AB Compounds of the formula ##STR1## wherein R.sup.1 includes alkyl, halo, nitro, amino, cyano, alkoxy, and alkoxycarbonyl; R.sup.2 is alkyl and substituted alkyl; and R.sup.3 is OH or NHOH are useful for inhibiting matrix metalloproteinase enzymes in animals, and as such, prevent and treat diseases resulting from the breakdown of connective tissues.

AN 1998:57969 USPATFULL

TI Biphenysulfonamide matrix metal alloproteinase inhibitors

IN O'Brien, Patrick Michael, Stockbridge, MI, United States
Sliskovic, Drago Robert, Saline, MI, United States

PA Warner-Lambert Company, Morris Plains, NJ, United States (U.S. corporation)

PI US 5756545 19980526 <--

AI US 1997-844598 19970421 (8)

DT Utility

FS Granted

EXNAM Primary Examiner: Barts, Samuel

LREP Ashbrook, Charles W.

CLMN Number of Claims: 18

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 700

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5756545 19980526 <--

DETD (S)-2-(4'-Bromo-biphenyl-4-sulfonylamino)-**3-phenyl-propionic Acid**

DETD (S)-(4'-Isopropyl-biphenyl-4-sulfonylamino)-**3-phenyl-propionic Acid**

DETD As **matrix metalloproteinase inhibitors**, the compounds of Formula I are useful as agents for the treatment of multiple sclerosis. They are also useful as. . .

CLM What is claimed is:
8. A compound of claim 7 which is (S)-2-(4'-bromo-biphenyl-4-sulfonylamino)-**3-phenyl-propionic acid**, or (S)-(4'-isopropyl-biphenyl-4-sulfonylamino)-**3-phenyl-propionic acid**.

inventor search

FILE 'EMBASE' ENTERED AT 18:47:25 ON 22 JUL 2002


FILE 'BIOSIS' ENTERED AT 18:47:25 ON 22 JUL 2002


FILE 'CAPLUS' ENTERED AT 18:47:25 ON 22 JUL 2002
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FILE 'USPATFULL' ENTERED AT 18:47:25 ON 22 JUL 2002


=> s deleve,l?/au
L1 82 DELEVE,L?/AU

=> s l1 and hepatic
L2 44 L1 AND HEPATIC

=> dup rem l2
PROCESSING COMPLETED FOR L2
L3 28 DUP REM L2 (16 DUPLICATES REMOVED)

=> d l3 1-28

L3 ANSWER 1 OF 28 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 2002102858 EMBASE
TI Toxic injury to **hepatic** sinusoids: Sinusoidal obstruction syndrome (veno-occlusive disease).
AU **DeLeve L.D.**; Shulman H.M.; McDonald G.B.
CS Dr. G.B. McDonald, Gastroenterology Section, Fred Hutchinson Cancer Res. Ctr., 1100 Fairview Avenue North, Seattle, WA 98109-1024, United States
SO Seminars in Liver Disease, (2002) 22/1 (27-41).
Refs: 189
ISSN: 0272-8087 CODEN: SLDIEE
CY United States
DT Journal; General Review
FS 005 General Pathology and Pathological Anatomy
006 Internal Medicine
037 Drug Literature Index
038 Adverse Reactions Titles
048 Gastroenterology
LA English
SL English

L3 ANSWER 2 OF 28 CAPLUS COPYRIGHT 2002 ACS
AN 2001:630408 CAPLUS
DN 136:318834
TI A single ethanol binge exacerbates early acetaminophen-induced centrilobular injury to the sinusoidal endothelium and alters sinusoidal blood flow
AU McCuskey, R. S.; Machen, N. W.; Wang, X.; McCuskey, M. K.; Abril, E.; Earnest, D. L.; **DeLeve, L. D.**
CS Departments of Cell Biology and Anatomy, College of Medicine, University of Arizona, Tucson, AZ, USA
SO Cells of the Hepatic Sinusoid (2001), 8, 68-70
CODEN: CHSIEL
PB Kupffer Cell Foundation
DT Journal

LA English
RE.CNT 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 3 OF 28 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 1
AN 2001327007 EMBASE
TI **Hepatic** venoocclusive disease: A major complication of hematopoietic stem cell transplantation in cancer patients.
AU **DeLeve L.D.**
CS Dr. L.D. DeLeve, USC Keck School of Medicine, 2011 Zonal Avenue-HMR 603, Los Angeles, CA 90293, United States. deleve@hsc.usc.edu
SO Tumori, (2001) 87/2 (S27-S29).
Refs: 26
ISSN: 0300-8916 CODEN: TUMOAB
CY Italy
DT Journal; Conference Article
FS 006 Internal Medicine
016 Cancer
037 Drug Literature Index
048 Gastroenterology
LA English

L3 ANSWER 4 OF 28 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2001:248876 BIOSIS
DN PREV200100248876
TI Toxin induced matrix metalloproteinases may damage **hepatic** sinusoidal integrity.
AU **DeLeve, Laurie D. (1)**; Tsai, Jeffrey; Wang, Peixin; Wang, Xiangdong (1); Park, Ji Min; Tokes, Zoltan A.
CS (1) Div. of Gastrointestinal and Liver Diseases, Dept. of Pathology, University of Southern California, 1303 N. Mission Road, Los Angeles, CA, 90033 USA
SO FASEB Journal, (March 7, 2001) Vol. 15, No. 4, pp. A26. print.
Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA March 31-April 04, 2001
ISSN: 0892-6638.
DT Conference
LA English
SL English

L3 ANSWER 5 OF 28 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2002:175859 BIOSIS
DN PREV200200175859
TI Prevention of **hepatic** venoocclusive disease in the rat by inhibition of matrix metalloproteinases.
AU **DeLeve, Laurie D. (1)**; Wang, Xiangdong (1); Tsai, Jeffrey (1); Kanel, Gary (1); Tokes, Zoltan (1)
CS (1) USC Keck Sch of Medicine, Los Angeles, CA USA
SO Gastroenterology, (April, 2001) Vol. 120, No. 5 Supplement 1, pp. A.54. http://www.gastrojournal.org/. print.
Meeting Info.: 102nd Annual Meeting of the American Gastroenterological Association and Digestive Disease Week Atlanta, Georgia, USA May 20-23, 2001
ISSN: 0016-5085.
DT Conference
LA English

L3 ANSWER 6 OF 28 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 2
AN 2000053804 EMBASE

TI Support of sinusoidal endothelial cell glutathione prevents **hepatic** veno-occlusive disease in the rat.
AU Wang X.; Kanel G.C.; **DeLeve L.D.**
CS Dr. L.D. DeLeve, Div. of Gastrointestinal/Liver Dis., USC Keck School of Medicine, 2011-Zonal Ave-HMR 603, Los Angeles, CA 90033, United States. deleve@hsc.usc.edu
SO Hepatology, (2000) 31/2 (428-434).
Refs: 10
ISSN: 0270-9139 CODEN: HPTLD
CY United States
DT Journal; Article
FS 030 Pharmacology
037 Drug Literature Index
048 Gastroenterology
LA English
SL English

L3 ANSWER 7 OF 28 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2000:294533 BIOSIS
DN PREV200000294533
TI Embolization by sinusoidal lining cells causes the congestion of **hepatic** venoocclusive disease.
AU **DeLeve, Laurie D. (1)**; Ito, Yoshiya; Machen, Nancy W.; McCuskey, Margaret K.; Wang, Xiangdong; McCuskey, Robert S.
CS (1) Univ of Southern CA, Los Angeles, CA USA
SO Gastroenterology, (April, 2000) Vol. 118, No. 4 Suppl. 2 Part 1, pp. AASLD
A100. print.
Meeting Info.: 101st Annual Meeting of the American Gastroenterological Association and the Digestive Disease Week San Diego, California, USA May 21-24, 2000 American Gastroenterological Association
. ISSN: 0016-5085.
DT Conference
LA English
SL English

L3 ANSWER 8 OF 28 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 3
AN 1999187494 EMBASE
TI Characterization of a reproducible rat model of **hepatic** veno-occlusive disease.
AU **DeLeve L.D.**; McCuskey R.S.; Wang X.; Hu L.; McCuskey M.K.; Epstein R.B.; Kanel G.C.
CS Dr. L.D. DeLeve, Div. of Gastrointestinal/Liver Dis., USC School of Medicine, 2011 Zonal Ave-HMR 603, Los Angeles, CA 90033, United States. deleve@hsc.usc.edu
SO Hepatology, (1999) 29/6 (1779-1791).
Refs: 36
ISSN: 0270-9139 CODEN: HPTLD
CY United States
DT Journal; Article
FS 005 General Pathology and Pathological Anatomy
048 Gastroenterology
LA English
SL English

L3 ANSWER 9 OF 28 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1999:500398 BIOSIS
DN PREV199900500398
TI Sinusoidal dissection and embolization blocks the **hepatic** microcirculation in **hepatic** venoocclusive disease (HVOD.

AU **Deleve, Laurie D. (1)**; Ito, Yoshiya; Machen, Nancy W.; McCuskey, Margaret K.; McCuskey, Robert S.
CS (1) USC School of Medicine, Los Angeles, CA USA
SO Hepatology, (Oct., 1999) Vol. 30, No. 4 PART 2, pp. 574A.
Meeting Info.: 50th Annual Meeting and Postgraduate Courses of the American Association for the Study of Liver Diseases Dallas, Texas, USA November 5-9, 1999 American Association for the Study of Liver Diseases
. ISSN: 0270-9139.
DT Conference
LA English

L3 ANSWER 10 OF 28 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1999:505564 BIOSIS
DN PREV199900505564
TI A single ethanol binge exacerbates early acetaminophen-induced centrilobular injury to the sinusoidal endothelium.
AU McCuskey, Robert S. (1); Machen, Nancy W. (1); Wang, Xiangdong; McCuskey, Margaret K. (1); **Deleve, Laurie D.**
CS (1) Univ of Arizona, Tucson, AZ USA
SO Hepatology, (Oct., 1999) Vol. 30, No. 4 PART 2, pp. 335A.
Meeting Info.: 50th Annual Meeting and Postgraduate Courses of the American Association for the Study of Liver Diseases Dallas, Texas, USA November 5-9, 1999 American Association for the Study of Liver Diseases
. ISSN: 0270-9139.
DT Conference
LA English

L3 ANSWER 11 OF 28 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1999:505736 BIOSIS
DN PREV199900505736
TI Decrease in **hepatic** nitric oxide production contributes to **hepatic** veno-occlusive disease (HVOD.
AU **Deleve, Laurie D. (1)**; Wang, Xiangdong (1)
CS (1) Univ of Southern CA, Los Angeles, CA USA
SO Hepatology, (Oct., 1999) Vol. 30, No. 4 PART 2, pp. 218A.
Meeting Info.: 50th Annual Meeting and Postgraduate Courses of the American Association for the Study of Liver Diseases Dallas, Texas, USA November 5-9, 1999 American Association for the Study of Liver Diseases
. ISSN: 0270-9139.
DT Conference
LA English

L3 ANSWER 12 OF 28 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1998:526112 BIOSIS
DN PREV199800526112
TI Characterization of a reproducible model of **hepatic** venoocclusive disease (HVOD.
AU **Deleve, L. D. (1)**; Wang, X. (1); McCuskey, R.; Kanel, G.
CS (1) Div. GI/Liver Dis., USC School Med., Los Angeles, CA USA
SO Hepatology, (Oct., 1998) Vol. 28, No. 4 PART 2, pp. 451A.
Meeting Info.: Biennial Scientific Meeting of the International Association for the Study of the Liver and the 49th Annual Meeting and Postgraduate Courses of the American Association for the Study of Liver Diseases Chicago, Illinois, USA November 4-10, 1998 International Association for the Study of the Liver
. ISSN: 0270-9139.
DT Conference
LA English

L3 ANSWER 13 OF 28 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

AN 1998:525948 BIOSIS
DN PREV199800525948
TI Support of sinusoidal endothelial cell (SEC) glutathione prevents **hepatic** venoocclusive disease in vivo.
AU Wang, Xiangdong (1); Kanel, Gary C.; **Deleve, Laurie D.**
CS (1) Div. Gastrointestinal Liver Diseases, USC Sch. Med., Los Angeles, CA USA
SO Hepatology, (Oct., 1998) Vol. 28, No. 4 PART 2, pp. 410A.
Meeting Info.: Biennial Scientific Meeting of the International Association for the Study of the Liver and the 49th Annual Meeting and Postgraduate Courses of the American Association for the Study of Liver Diseases Chicago, Illinois, USA November 4-10, 1998 International Association for the Study of the Liver
. ISSN: 0270-9139.
DT Conference
LA English

L3 ANSWER 14 OF 28 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 4
AN 1999008285 EMBASE
TI Glutathione defense in non-parenchymal cells.
AU **DeLeve L.D.**
CS Dr. L.D. DeLeve, University of Southern California, Health Science Campus-MMR 401, Division of GI/Liver Disease, 1333 San Pablo St., Los Angeles, CA 90033, United States
SO Seminars in Liver Disease, (1998) 18/4 (403-413).
Refs: 95
ISSN: 0272-8087 CODEN: SLDIEE
CY United States
DT Journal; General Review
FS 048 Gastroenterology
LA English
SL English

L3 ANSWER 15 OF 28 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 5
AN 97218169 EMBASE
DN 1997218169
TI Sinusoidal endothelial cells as a target for acetaminophen toxicity: Direct action versus requirement for hepatocyte activation in different mouse strains.
AU **DeLeve L.D.**; Wang X.; Kaplowitz N.; Shulman H.M.; Bart J.A.; Van der Hock A.
CS Dr. L.D. DeLeve, USC Health Science Campus, 1333 San Pablo St., Los Angeles, CA 90033, United States. deleve@hsc.usc.edu
SO Biochemical Pharmacology, (1997) 53/9 (1339-1345).
Refs: 38
ISSN: 0006-2952 CODEN: BCPCA6
PUI S 0006-2952(97)00048-8
CY United States
DT Journal; Article
FS 037 Drug Literature Index
048 Gastroenterology
052 Toxicology
LA English
SL English

L3 ANSWER 16 OF 28 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 6
AN 96306808 EMBASE
DN 1996306808
TI Cellular target of cyclophosphamide toxicity in the murine liver: Role of glutathione and site of metabolic activation.

AU **DeLeve L.D.**
CS Div. of GI/Liver Diseases, USC Health Science Campus, 1333 San Pablo St.,Los Angeles, CA 90033, United States
SO Hepatology, (1996) 24/4 I (830-837).
ISSN: 0270-9139 CODEN: HPTLD
CY United States
DT Journal; Article
FS 005 General Pathology and Pathological Anatomy
048 Gastroenterology
052 Toxicology
LA English
SL English

L3 ANSWER 17 OF 28 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 7
AN 96088710 EMBASE
DN 1996088710
TI Toxicity of azathioprine and monocrotaline in murine sinusoidal endothelial cells and hepatocytes: The role of glutathione and relevance to **hepatic** venoocclusive disease.
AU **DeLeve L.D.**; Wang X.; Kuhlenkamp J.F.; Kaplowitz N.
CS Division of GI/Liver Diseases, USC Health Science Campus, 1333 San Pablo St.,Los Angeles, CA 90033, United States
SO Hepatology, (1996) 23/3 (589-599).
ISSN: 0270-9139 CODEN: HPTLD
CY United States
DT Journal; Article
FS 005 General Pathology and Pathological Anatomy
048 Gastroenterology
LA English
SL English

L3 ANSWER 18 OF 28 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1996:133628 BIOSIS
DN PREV199698705763
TI Mechanisms of drug-induced liver disease.
AU **Deleve, Laurie D. (1)**; Kaplowitz, Neil
CS (1) Univ. Southern Calif., Div. Gastrointestinal Liver Dis., 1333 San Pablo Street-MMR 408, Los Angeles, CA 90033 USA
SO Gastroenterology Clinics of North America, (1995) Vol. 24, No. 4, pp. 787-810.
ISSN: 0889-8553.
DT General Review
LA English

L3 ANSWER 19 OF 28 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 8
AN 95118903 EMBASE
DN 1995118903
TI Differential toxicity of the protein phosphatase inhibitors microcystin and calyculin A.
AU Runnegar M.T.; Maddatu T.; **Deleve L.D.**; Berndt N.; Govindarajan S.
CS Div. of Gastrointestinal/Liver Dis., MUDD 401, USC School of Medicine, 1333 San Pablo Street,Los Angeles, CA 90033, United States
SO Journal of Pharmacology and Experimental Therapeutics, (1995) 273/1 (545-553).
ISSN: 0022-3565 CODEN: JPETAB
CY United States
DT Journal; Article
FS 030 Pharmacology
037 Drug Literature Index

LA English
SL English

L3 ANSWER 20 OF 28 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 9
AN 94105211 EMBASE
DN 1994105211
TI Dacarbazine toxicity in murine liver cells: A model of **hepatic** endothelial injury and glutathione defense.
AU **Deleve L.D.**
CS Division of GI and Liver Diseases, MMR 408, University of Southern California, San Pablo St.,Los Angeles, CA 90033, United States
SO Journal of Pharmacology and Experimental Therapeutics, (1994) 268/3 (1261-1270).
ISSN: 0022-3565 CODEN: JPETAB
CY United States
DT Journal; Article
FS 005 General Pathology and Pathological Anatomy
037 Drug Literature Index
038 Adverse Reactions Titles
052 Toxicology
LA English
SL English

L3 ANSWER 21 OF 28 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1994:333676 BIOSIS
DN PREV199497346676
TI The effects of the protein phosphatase inhibitors microcystin and calyculin A differ in hepatocytes and **hepatic** endothelial cells.
AU Runnegar, M. T. C.; **Deleve, L.**; Berndt, N.
CS Dep. Med., Univ. Southern California, Los Angeles, CA 90033 USA
SO FASEB Journal, (1994) Vol. 8, No. 7, pp. A1231.
Meeting Info.: 85th Annual Meeting of the American Society for Biochemistry and Molecular Biology Washington, D.C., USA May 21-25, 1994
ISSN: 0892-6638.
DT Conference
LA English

L3 ANSWER 22 OF 28 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1995:2724 BIOSIS
DN PREV199598017024
TI New insights into the pathogenesis of HVOD: Hepatocytes are required for cyclophosphamide toxicity to sinusoidal endothelial cells (SEC.
AU **Deleve, L. D.**; Huybrechts, M. E.; Kaplowitz, N.
CS Div. GI/Liver, USC, Los Angeles, CA 90033 USA
SO Hepatology, (1994) Vol. 20, No. 4 PART 2, pp. 188A.
Meeting Info.: 45th Annual Meeting of the American Association for the Study of Liver Diseases Chicago, Illinois, USA November 11-15, 1994
ISSN: 0270-9139.
DT Conference
LA English

L3 ANSWER 23 OF 28 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1993:354543 BIOSIS
DN PREV199345037968
TI Agents causing **hepatic** venoocclusive disease (HVOD) selectively kill sinusoidal endothelial cells (SECs): Common mechanism through GSH depletion.
AU **Deleve, L. D.**; Kuhlenkamp, J. F.
CS Div. GI/Liver Diseases, USC, Los Angeles, CA 90033 USA
SO Gastroenterology, (1993) Vol. 104, No. 4 SUPPL., pp. A894.

Meeting Info.: 94th Annual Meeting of the American Gastroenterological Association Boston, Massachusetts, USA May 15-21, 1993
ISSN: 0016-5085.
DT Conference
LA English

L3 ANSWER 24 OF 28 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC. DUPLICATE 10
AN 1993:106638 BIOSIS
DN PREV199344049038
TI Regulation of **hepatic** glutathione.
AU Fernandez-Checa, Jose C.; Lu, Shelly; Ookhtens, Murad; **Deleve, Laurie**; Runnegar, Maria; Yoshida, Haruhiko; Saiki, Hideki; Kannan, Ram; Maddatu, Terry; et al.
CS Div. Gastrointestinal Liver Dis., Dep. Med., LAC 11-221, USC Sch. Med., Los Angeles, Calif. 90033
SO Tavoloni, N. [Editor]; Berk, P. D. [Editor]. (1993) pp. 363-395. Hepatic transport and bile secretion: Physiology and pathophysiology.
Publisher: Raven Press 1185 Avenue of the Americas, New York, New York 10036-2806, USA.
ISBN: 0-88167-960-7.
DT Article
LA English

L3 ANSWER 25 OF 28 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1992:204107 BIOSIS
DN BR42:97182
TI SELECTIVE SUSCEPTIBILITY OF **HEPATIC** ENDOTHELIAL CELLS TO DACARBAZINE TOXICITY A MODEL FOR **HEPATIC** VENO-OCCLUSIVE DISEASE.
AU **DELEVE L D**; KAPLOWITZ N
CS DIV. GASTROINTESTINAL LIVER DIS., UNIV. SOUTHERN CALIF. SCH. MED., LOS ANGELES, CALIF. 90033.
SO KEYSTONE SYMPOSIUM ON THE MOLECULAR BIOLOGY OF THE ENDOTHELIAL CELL, KEYSTONE, COLORADO, USA, JANUARY 13-19, 1992. J CELL BIOCHEM SUPPL. (1992)
0 (16 PART A), 42.
CODEN: JCBSD7.
DT Conference
FS BR; OLD
LA English

L3 ANSWER 26 OF 28 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1992:41056 BIOSIS
DN BR42:17206
TI SELECTIVE SUSCEPTIBILITY OF **HEPATIC** ENDOTHELIAL CELLS TO DACARBAZINE TOXICITY A MODEL FOR **HEPATIC** VENO-OCCLUSIVE DISEASE.
AU **DELEVE L D**; KAPLOWITZ N
CS DIV. GI/LIVER, USC SCH. MED., LOS ANGELES, CALIF.
SO 42ND ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES, CHICAGO, ILLINOIS, USA, NOVEMBER 2-5, 1991. HEPATOLOGY. (1991) 14 (4 PART 2), 161A.
CODEN: HPTLD9. ISSN: 0270-9139.
DT Conference
FS BR; OLD
LA English

L3 ANSWER 27 OF 28 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1991:64280 BIOSIS
DN BR40:29635

TI **HEPATIC** ENDOTHELIAL CELLS AS A TARGET FOR ACETAMINOPHEN APAP TOXICITY.
AU **DELEVE L D**; KAPLOWITZ N
CS DIV. GASTROENTEROL. AND LIVER DISEASES, UNIV. SOUTHERN CALIF., LOS ANGELES, CALIF.
SO 41ST ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES, CHICAGO, ILLINOIS, USA, NOVEMBER 3-6, 1990. HEPATOLOGY. (1990) 12 (4 PART 2), 1009.
CODEN: HPTLD9. ISSN: 0270-9139.
DT Conference
FS BR; OLD
LA English

L3 ANSWER 28 OF 28 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 11
AN 91017672 EMBASE
DN 1991017672
TI Importance and regulation of **hepatic** glutathione.
AU **Deleve L.D.**; Kaplowitz N.
CS University of Southern California School of Medicine, Department of Medicine, 2025 Zonal Ave., Los Angeles, CA 90033, United States
SO Seminars in Liver Disease, (1990) 10/4 (251-266).
ISSN: 0272-8087 CODEN: SLDIEE
CY United States
DT Journal; Article
FS 048 Gastroenterology
030 Pharmacology
037 Drug Literature Index
LA English

=> d 17-18 ab

L3 ANSWER 17 OF 28 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 7
AB The mechanisms leading to **hepatic** venoocclusive disease (HVOD) remain largely unknown. Azathioprine and monocrotaline were studied as part of a series of studies looking at a variety of toxins that induce HVOD to find common features that might be of pathogenic significance. In a previous study, dacarbazine showed selective in vitro toxicity to sinusoidal endothelial cells (SEC) compared with hepatocytes and a key role for SEC glutathione (GSH) was demonstrated. Murine SEC and hepatocytes were isolated and studied in culture. Azathioprine and monocrotaline were found to be selectively more toxic to SEC than to hepatocytes. The relative resistance of hepatocytes to azathioprine was due to enhanced GSH defense: hepatocytes exposed to azathioprine maintained intracellular GSH levels better than SEC, particularly when supplemental GSH precursors were added, and hepatocyte resistance was completely overcome by depletion of intracellular GSH. In contrast, monocrotaline toxicity in hepatocytes was largely unaffected by depletion of GSH, which suggests that selectivity of monocrotaline for SEC may be attributable to differences in metabolic activation. Both compounds are detoxified by GSH in SEC, as demonstrated by enhanced toxicity in the presence of buthionine sulfoximine (BSO) and attenuation of toxicity with exogenous GSH. SEC GSH levels were more than 70% to 80% depleted by monocrotaline and azathioprine, respectively, before cell death. Azathioprine and monocrotaline are selectively toxic to SEC; the mechanism of toxicity in the SEC may be caused by profound GSH depletion.

L3 ANSWER 18 OF 28 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

=> d 12 ab

L3 ANSWER 12 OF 28 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

=> d 22 ab

L3 ANSWER 22 OF 28 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

=> d 4-5 ab

L3 ANSWER 4 OF 28 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AB Monocrotaline (MCT), a pyrrolizidine alkaloid, is a prototypical toxin that causes **hepatic** venoocclusive disease (VOD). An important early event in monocrotaline-induced VOD is the rounding up of sinusoidal endothelial cells with subsequent dissection of the sinusoidal lining, which embolizes into the sinusoids. These events precede the clinical manifestations of VOD which occur 72 hrs after MCT treatment. The loss of sinusoidal integrity suggests a possible role for matrix metalloproteinases (MMPs). This study examines whether MMPs contribute to sinusoidal damage by MCT. Sprague-Dawley rats, 270 g, were treated with 160mg/kg MCT i.g. on day 0. For MMP inhibition studies, rats were given 15mg/kg doxycycline (DOX) b.i.d. starting 48 hrs prior to the MCT treatment. Measurements of MMP mRNA and activity were done 48 hrs after MCT treatment (day 2). MMP mRNA synthesis was assessed by RT-PCR and Taqman assays. MMP activity in liver was measured by zymography. Ten to 17-fold increase in MMP-9 activity was detected by zymography on day 2 compared to control liver, whereas increase in MMP-2 were less than two fold. MMP-9 mRNA levels detected by RT-PCR and Taqman were 4 to 24 folds higher on day 2 than in controls. DOX treatment prevented histologic evidence of VOD on days 4 and 6. DOX analogues that do not inhibit MMPs had little or no effect on VOD. DOX did not alter total MMP-9 and MMP-2 levels determined by zymography indicating that the drug did not inhibit MMP synthesis. Note that zymography conditions dissociate enzyme-inhibitor complexes and cannot detect the effect of inhibitors on enzymes. These data suggest that in MCT-induced VOD, increased MMP-9 activity may contribute to the destruction of **hepatic** sinusoids.

L3 ANSWER 5 OF 28 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

=>

N' IS NOT A VALID FIELD CODE
'RN' IS NOT A VALID FIELD CODE
'RN' IS NOT A VALID FIELD CODE
L6 7 193807-58-8/RN

=> dup rem l6
PROCESSING COMPLETED FOR L6
L7 7 DUP REM L6 (0 DUPLICATES REMOVED)

=> d l7 1-7 ab bib kwic

L7 ANSWER 1 OF 7 USPATFULL
AB Compounds having a metalloproteinase inhibitory activity, represented by
the formula (I), its optically active isomers, their pharmaceutically acceptable salts, or hydrates thereof. ##STR1##
AN 2001:75420 USPATFULL
TI Sulfonated amino acid derivatives and metalloproteinase inhibitors containing the same
IN Wantanabe, Fumihiko, Nara, Japan
Tsuzuki, Hiroshige, Kyoto, Japan
Ohtani, Mitsuaki, Nara, Japan
PA Shionogi & Co., Ltd., Osaka, Japan (non-U.S. corporation)
PI US 6235768 B1 20010522
AI US 1999-307818 19990510 (9)
RLI Division of Ser. No. US 1998-120197, filed on 22 Jul 1998
PRAI JP 1996-30082 19960123
JP 1996-213555 19960813
DT Utility
FS Granted
EXNAM Primary Examiner: Powers, Fiona T.
LREP Foley & Lardner
CLMN Number of Claims: 10
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 2705
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT 56176-31-9P 130633-87-3P 177583-41-4P 188006-04-4P 188006-06-6P
188006-15-7P 188006-26-0P **193807-58-8P** 193807-60-2P
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(prepn. of sulfonylamino acid derivs. as metalloproteinase inhibitors)

L7 ANSWER 2 OF 7 USPATFULL

AB Compounds having a metalloproteinase inhibitory activity, represented by the formula (I), its optically active isomers, their pharmaceutically acceptable salts, or hydrates thereof. ##STR1##

AN 2001:44256 USPATFULL

TI Sulfonated amino acid derivatives and metalloproteinase inhibitors containing the same

IN Wantanabe, Fumihiko, Kitakatsuragi-gun, Japan
Tsuzuki, Hiroshige, Tsuzuki-gun, Japan
Ohtani, Mitsuaki, Nara, Japan
PA Shionogi & Co., Ltd., Osaka, Japan (non-U.S. corporation)

PI US 6207698 B1 20010327
AI US 1998-120197 19980722 (9)
RLI Continuation of Ser. No. WO 1997-JP126, filed on 22 Jan 1997
PRAI JP 1996-30082 19960123
JP 1996-213555 19960813
DT Utility
FS Granted
EXNAM Primary Examiner: Powers, Fiona T.
LREP Foley & Lardner
CLMN Number of Claims: 19
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 2679

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT 56176-31-9P 130633-87-3P 177583-41-4P 188006-04-4P 188006-06-6P
188006-15-7P 188006-26-0P **193807-58-8P** 193807-60-2P
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(prepn. of sulfonylamino acid derivs. as metalloproteinase inhibitors)

L7 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2002 ACS

AB Title compds. (R)-R5R4R3SO2N(R2)CH(R1)COY [I; R1 and R2 each represents hydrogen, optionally substituted lower alkyl, optionally substituted (hetero)aryl, etc.; R3 represents optionally substituted (hetero)arylene, etc.; R4 represents, e.g., a single bond, CC, or a group represented by Q,

R5 represents optionally substituted (hetero)aryl, optionally substituted nonarom. heterocyclic group, etc.; and Y represents NHOH or OH], stereoisomers, pharmacol. acceptable salts, and hydrates are prepd. as remedial or preventive agents for congestive heart failure in mammal. The

title compd. (S)-II was prepd.

AN 2000:190916 CAPLUS

DN 132:236806

TI Preparation of remedial or preventive agents for congestive heart failure

IN Watanabe, Fumihiko; Gemba, Takefumi; Tsuzuki, Hiroshige; Shimamura, Toshitake

PA Shionogi & Co., Ltd., Japan

SO PCT Int. Appl., 69 pp.

CODEN: PIXXD2
DT Patent
LA Japanese
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | WO 2000015213 | A1 | 20000323 | WO 1999-JP4859 | 19990908 |

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

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| | AU 9956470 | A1 | 20000403 | AU 1999-56470 | 19990908 |
| PRAI | JP 1998-258033 | A | 19980911 | | |
| | WO 1999-JP4859 | W | 19990908 | | |

RE.CNT 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT

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| 56176-31-9P | 70136-17-3P | 130633-87-3P | 140645-36-9P | 177583-41-4P |
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220043-29-8P 220043-30-1P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of remedial or preventive agents for congestive heart failure)

L7 ANSWER 4 OF 7 USPATFULL
AB Compounds having a metalloproteinase inhibitory activity, represented by the formula (I), its optically active isomers, their pharmaceutically acceptable salts, or hydrates thereof. ##STR1##
AN 2000:157443 USPATFULL
TI Sulfonated amino acid derivatives and metalloproteinase inhibitors containing the same
IN Watanabe, Fumihiko, Nara, Japan
Tsuzuki, Hiroshige, Kyoto, Japan
Ohtani, Mitsuaki, Nara, Japan
PA Shionogi & Co., Ltd., Osaka, Japan (non-U.S. corporation)
PI US 6150394 20001121
AI US 1998-120378 19980722 (9)
RLI Continuation of Ser. No. WO 1997-JP126, filed on 22 Jan 1997
PRAI JP 1996-30082 19960123
JP 1996-213555 19960813
DT Utility
FS Granted
EXNAM Primary Examiner: Barts, Samuel
LREP Foley & Lardner
CLMN Number of Claims: 12
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 3197
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT 56176-31-9P 130633-87-3P 177583-41-4P 188006-04-4P 188006-06-6P
188006-15-7P 188006-26-0P **193807-58-8P** 193807-60-2P
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193810-13-8P 193810-14-9P 193810-15-0P 193810-16-1P 193810-17-2P
(prepn. of sulfonylamino acid derivs. as metalloproteinase inhibitors)

L7 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2002 ACS
AB The title compds. R4R3SO2N(R2)CH(R1)COY [R1 = (un)substituted alkyl, etc.;
R2 = H, alkyl, etc.; R3 = phenylene, etc.; R4 = (un)substituted phenyl; Y = NHOH, OH] are prepd. The title compd. I at 1000 nM gave 97.6% inhibition of MMP-8. Formulations are given.
AN 1999:579153 CAPLUS
DN 131:214280
TI Preparation of sulfonamides as MMP-8 inhibitors
IN Watanabe, Fumihiko; Tsumiki, Hiroshige
PA Shionogi and Co., Ltd., Japan
SO Jpn. Kokai Tokkyo Koho, 28 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
FAN.CNT 1

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| PI JP 11246527 | A2 | 19990914 | JP 1998-49260 | 19980302 |

OS MARPAT 131:214280
IT 130633-87-3P 140645-36-9P **193807-58-8P** 193807-60-2P
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220043-32-3P 220043-34-5P 220043-40-3P 220043-41-4P 226409-65-0P

243143-79-5P 243143-80-8P 243143-81-9P 243143-82-0P 243143-83-1P
243143-84-2P 243143-85-3P 243143-86-4P 243143-87-5P 243143-88-6P
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243144-05-0P 243144-06-1P 243144-07-2P 243144-08-3P 243144-09-4P
243144-10-7P 243144-11-8P 243144-12-9P 243144-13-0P 243144-14-1P
243144-15-2P 243144-16-3P 243144-17-4P 243144-18-5P 243144-93-6P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological
study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);
BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of sulfonamides as MMP-8 inhibitors)

L7 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2002 ACS

AB Various N-sulfonylamino acid derivs., e.g. I (R1 = PhCH2, X = bond, Y = SO2, CO, Z = CONHOH, CO2H; R1 = indol-3-ylmethyl, X = bond, Y = SO2, Z = CONHOH, CO2H; R1 = Me2CH, X = O, Y = SO2, Z = CONHOH, CO2H) and II (R2 = indol-3-ylmethyl, R5 = H, OMe-4, OMe-3, A = CH:CH, X = bond; R2 = indol-3-ylmethyl, R5 = Me-4, A = S, X = bond; R2 = CHMe2, R5 = OMe-4, SMe-4, A = CH:CH, X = bond; R2 = CHMe2, R5 = OMe-4, A = S, X = bond; R2 = indol-3-ylmethyl, R5 = H, Me-4, CO2H-4, A = CH:CH, X = C.tplbond.C; R2 = indol-3-ylmethyl, R5 = NO2-2, NO2-4, Me-4, A = S, X = C.tplbond.C; R2 = CHMe2, R5 = Me-4, A = CH:CH, S, X = C.tplbond.C; R2 = CH2Ph, R5 = OMe-4, A = CH:CH, S, X = C.tplbond.C), were synthesized and evaluated for their in vitro and in vivo activities to inhibit type IV collagenase (MMP-9 and MMP-2). When the amino acid residue and the sulfonamide moiety were modified, their inhibitory activities were greatly affected by the structure of the sulfonamide moiety. A series of aryl sulfonamide derivs. contg. biaryl, tetrazole, amide, and triple bond were found to be potent and highly selective inhibitors of MMP-9 and MMP-2. In addn., these compds. were orally active in animal models of tumor growth and metastasis. These results revealed the potential of the N-sulfonylamino acid derivs. as a new type of candidate drug for the treatment of cancer.

AN 1998:66723 CAPLUS

DN 128:188290

TI Highly Selective and Orally Active Inhibitors of Type IV Collagenase (MMP-9 and MMP-2): N-Sulfonylamino Acid Derivatives

AU Tamura, Yoshinori; Watanabe, Fumihiko; Nakatani, Takuji; Yasui, Ken; Fuji, Masahiro; Komurasaki, Tadafumi; Tsuzuki, Hiroshige; Maekawa, Ryuji; Yoshioka, Takayuki; Kawada, Kenji; Sugita, Kenji; Ohtani, Mitsuaki

CS Shionogi Research Laboratories, Shionogi Co. Ltd., Osaka, 553, Japan

SO Journal of Medicinal Chemistry (1998), 41(4), 640-649
CODEN: JMCMAR; ISSN: 0022-2623

PB American Chemical Society

DT Journal

LA English

IT 140645-35-8P 140645-36-9P 188006-04-4P 188006-06-6P 188006-15-7P
188006-42-0P **193807-58-8P** 193807-60-2P 193808-50-3P
193808-54-7P 193808-61-6P 193808-69-4P 193809-24-4P 193809-27-7P
193809-30-2P 193809-31-3P 193809-35-7P 193809-37-9P 193809-42-6P
193809-50-6P 193809-54-0P 193809-67-5P 193809-74-4P 193809-82-4P
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203640-27-1P 203640-34-0P 203640-36-2P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological
study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);
BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of N-sulfonylamino acid derivs. as orally active type IV collagenase inhibitors)

L7 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2002 ACS

AB The title compds. R5R4R3SO2NR2CHR1COY [R1 = (un)substituted alkyl, aryl, aralkyl, heteroaryl, etc.; R2 = H, (un)substituted alkyl, etc.; R3 = single bond, (un)substituted arylene, etc.; R4 = single bond, CH:CH, C.tplbond.C, CO, CONH, N:N, NHCONH, NHCO, O, S, SO2NH, etc.; R5 = (un)substituted alkyl, cycloalkyl, etc.; Y = NHOH, OH; a proviso is given]
are prepd. The title compd. (R)-I in vitro showed IC50 of 3.95 .mu.M against MMP-9 (gelatinase B).

AN 1997:513624 CAPLUS
DN 127:162119

TI Preparation of N-sulfonylamino acid derivatives as metalloproteinase inhibitors

IN Watanabe, Fumihiko; Tsuzuki, Hiroshige; Ohtani, Mitsuaki
PA Shionogi and vCo., Ltd., Japan; Watanabe, Fumihiko; Tsuzuki, Hiroshige; Ohtani, Mitsuaki

SO PCT Int. Appl., 128 pp.
CODEN: PIXXD2
DT Patent
LA Japanese

FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | WO 9727174 | A1 | 19970731 | WO 1997-JP126 | 19970122 |
| | W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| | RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| | CA 2242416 | AA | 19970731 | CA 1997-2242416 | 19970122 |
| | AU 9713195 | A1 | 19970820 | AU 1997-13195 | 19970122 |
| | AU 715764 | B2 | 20000210 | | |
| | CN 1214041 | A | 19990414 | CN 1997-193226 | 19970122 |
| | BR 9707010 | A | 19990720 | BR 1997-7010 | 19970122 |
| | EP 950656 | A1 | 19991020 | EP 1997-900747 | 19970122 |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| | JP 2001316254 | A2 | 20011113 | JP 2001-69135 | 19970122 |
| | NO 9803376 | A | 19980914 | NO 1998-3376 | 19980722 |
| | US 6150394 | A | 20001121 | US 1998-120378 | 19980722 |
| | US 6207698 | B1 | 20010327 | US 1998-120197 | 19980722 |
| | US 6235768 | B1 | 20010522 | US 1999-307818 | 19990510 |
| | AU 738793 | B2 | 20010927 | AU 2000-30222 | 20000501 |
| PRAI | JP 1996-30082 | A | 19960123 | | |
| | JP 1996-213555 | A | 19960813 | | |
| | JP 1997-526728 | A3 | 19970122 | | |
| | WO 1997-JP126 | W | 19970122 | | |
| | US 1998-120197 | A3 | 19980722 | | |

OS MARPAT 127:162119

IT 56176-31-9P 130633-87-3P 177583-41-4P 188006-04-4P 188006-06-6P
188006-15-7P 188006-26-0P **193807-58-8P** 193807-60-2P
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RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of sulfonylamino acid derivs. as metalloproteinase inhibitors)

=>

L39 ANSWER 1 OF 2 USPATFULL

AB In accordance with the present invention, there are provided conjugates of nitric oxide scavengers (e.g., dithiocarbamates, or "DC") and pharmacologically active agents (e.g., NSAIDs). Invention conjugates provide a new class of pharmacologically active agents (e.g., anti-inflammatory agents) which cause a much lower incidence of side-effects due to the protective effects imparted by modifying the pharmacologically active agents as described herein. In addition, invention conjugates are more effective than unmodified pharmacologically active agents because cells and tissues contacted by the pharmacologically active agent(s) are protected from the potentially damaging effects of nitric oxide overproduction induced thereby as a result of the co-production of nitric oxide scavenger (e.g., dithiocarbamate), in addition to free pharmacologically active agent, when invention conjugate is cleaved.

AN 1999:72602 USPATFULL

TI Conjugates of dithiocarbamates with pharmacologically active agents and uses therefore

IN Lai, Ching-San, Encinitas, CA, United States

PA Medinox, Inc., San Diego, CA, United States (U.S. corporation)

PI US 5916910 19990629 <--

AI US 1997-869158 19970604 (8)

DT Utility

FS Granted

EXNAM Primary Examiner: Davis, Zinna Northington

LREP Reiter, Esq., Stephen E.Gray, Cary, Ware & Freidenrich

CLMN Number of Claims: 27

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 1842

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L39 ANSWER 2 OF 2 USPATFULL

AB The invention provides conjugates of cis-docosahexaenoic acid and taxanes useful in treating cell proliferative disorders. Conjugates of paclitaxel and docetaxel are preferred.

AN 1998:98932 USPATFULL

TI DHA-pharmaceutical agent conjugates of taxanes

IN Shashoua, Victor E., Brookline, MA, United States
Swindell, Charles S., Merion, PA, United States
Webb, Nigel L., Bryn Mawr, PA, United States
Bradley, Matthews O., Laytonsville, MD, United States

PA Neuromedica, Inc., Conshohocken, PA, United States (U.S. corporation)

PI US 5795909 19980818 <--

AI US 1996-651312 19960522 (8)

DT Utility

FS Granted

EXNAM Primary Examiner: Jarvis, William R. A.

LREP Wolf, Greenfield & Sacks, P.C.

CLMN Number of Claims: 12

ECL Exemplary Claim: 1

DRWN 27 Drawing Figure(s); 14 Drawing Page(s)

LN.CNT 2451

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d 1-2 kwic

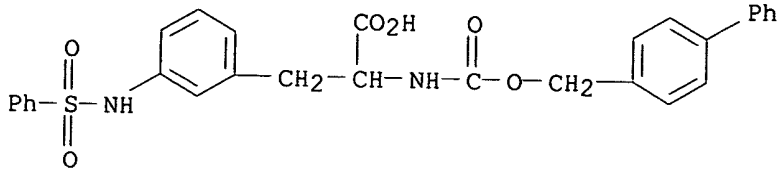
L39 ANSWER 1 OF 2 USPATFULL

PI US 5916910 19990629 <--
SUMM . . . motility disorders, obesity, hyperphagia, solid tumors (e.g., neuroblastoma), malaria, hematologic cancers, myelofibrosis, lung injury, graft-versus-host disease, head injury, CNS trauma, **hepatitis**, renal failure, liver disease (e.g., chronic **hepatitis** C), drug-induced lung injury (e.g., paraquat), myasthenia gravis (MG), ophthalmic diseases, post-angioplasty, restenosis, angina, coronary artery disease, and the like.
SUMM . . . erythromycins (e.g., erythromycin ethylsuccinate, erythromycin, erythromycin estolate, erythromycin lactobionate, erythromycin siearate, erythromycin ethylsuccinate, and the like), tetracyclines (e.g., tetracycline hydrochloride, **doxycycline** hyclate, minocycline hydrochloride, and the like), and the like);
SUMM . . . antibody therapeutics, murine MAb (e.g., anti-SLE vaccine, and MAb 3E10), primatized anti-CD4 antibodies (e.g., CE9.1), protease inhibitors (e.g., matrix metalloprotease (**MMP**) **inhibitors**, and stromelysin), protein synthesis antagonists (e.g., anti-CD6-bR, anti-T12-bR, and oncolysin CD6), purine nucleoside phosphorylase inhibitors (e.g., BCX-25, and BCX-14), selectin. . .
SUMM . . . cimetidine, ciprofloxacin, cisapride, clarithromycin, clavulanate, clonazepam, clotrimazole, codeine, conjugated estrogens, cyclobenzaprine, desogestrel, dexrazoxane, diazepam, dicyclomine HCI, digoxin, diltiazem, dirithromycin, doxazosin, **doxycycline**, enalapril, erythromycin, erythromycin base, erythromycin stearate, estradiol, ethinyl estradiol, ethynodiol diacetate, etodolac, famotidine, fluconazole, fluoxetine, fluvastatin, furosemide, gemfibrozil, glipizide, glyburide,. . .

L39 ANSWER 2 OF 2 USPATFULL
PI US 5795909 19980818 <--
DETD . . . Coumermycin Sodium; Cyclacillin; Cycloserine; Dalfopristin; Dapsone; Daptomycin; Demeclocycline; Demeclocycline Hydrochloride; Demecycline; Denofungin; Diaveridine; Dicloxacillin; Dicloxacillin Sodium; Dihydrostreptomycin Sulfate; Dipyrithione; Dirithromycin; **Doxycycline**; **Doxycycline** Calcium; **Doxycycline** Fosfatex; **Doxycycline** Hyclate; Droxacin Sodium; Enoxacin; Epicillin; Epitetracycline Hydrochloride; Erythromycin; Erythromycin Acistrate; Erythromycin Estolate; Erythromycin Ethylsuccinate; Erythromycin Gluceptate; Erythromycin Lactobionate; Erythromycin Propionate;. . .
DETD . . . lombricine; lometrexol; lonidamine; losoxantrone; lovastatin; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocol; maspin; matrilysin inhibitors; **matrix metalloproteinase inhibitors**; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin. . .
DETD . . . (Micrurus Fulvius); Antivenin (Crotalidae) Polyvalent; BCG Vaccine; Botulism Antitoxin; Cholera Vaccine; Diphtheria Antitoxin; Diphtheria Toxoid; Diphtheria Toxoid Adsorbed; Globulin, Immune; **Hepatitis** B Immune Globulin; **Hepatitis** B Virus Vaccine Inactivated; Influenza Virus Vaccine; Measles Virus Vaccine Live; Meningococcal Polysaccharide Vaccine Group A; Meningococcal Polysaccharide Vaccine Group. . .

=>

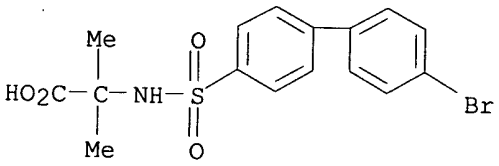
```
         28006 PROPIONIC
       5473436 ACID
          7807 ACIDS
       5479119 ACID
                 (ACID OR ACIDS)
L1       27829 PROPIONIC ACID
                 (PROPIONIC(W)ACID)

=> s biphenyl
L2      283086 BIPHENYL

=> s l1 and l2
L3         389 L1 AND L2

=> s sulphonyl or sulfonyl
            90 SULPHONYL
        740670 SULFONYL
             1 SULFONYLS
        740670 SULFONYL
                 (SULFONYL OR SULFONYLS)
L4      740690 SULPHONYL OR SULFONYL

=> s l3 and l4
L5          12 L3 AND L4

=> s amino
       3710800 AMINO
          8625 AMINOS
L6     3710800 AMINO
                 (AMINO OR AMINOS)

=>  s l5 and l6
L7           8 L5 AND L6

=> s 2-
L8      350825 2-

=> s l7 and l8
L9           0 L7 AND L8

=> d l7 1-8

L7   ANSWER 1 OF 8  REGISTRY  COPYRIGHT 2002 ACS
RN   361457-69-4  REGISTRY
CN   Phenylalanine, N-[([1,1'-biphenyl]-4-ylmethoxy)carbonyl]-3-
     [(phenylsulfonyl)amino]- (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   3-(3-Benzenesulfonylaminophenyl)-2-(biphenyl-4-
     ylmethoxycarbonylamino)propionic acid
FS   3D CONCORD
MF   C29 H26 N2 O6 S
SR   CA
LC   STN Files:   CA, CAPLUS, USPATFULL
```



**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

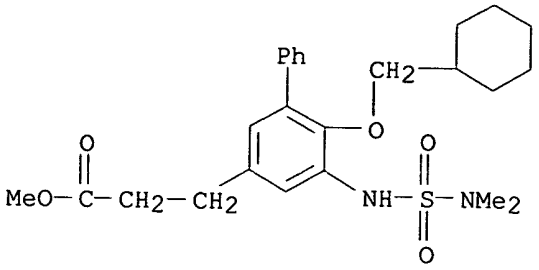
L7 ANSWER 2 OF 8 REGISTRY COPYRIGHT 2002 ACS
RN 326499-77-8 REGISTRY
CN **Alanine, N-[(4'-bromo[1,1'-biphenyl]-4-yl)sulfonyl]-2-methyl-(9CI)** (CA INDEX NAME)
OTHER NAMES:
CN **2-(4'-Bromobiphenyl-4-sulfonylamino)-2-methylpropionic acid**
FS 3D CONCORD
MF C16 H16 Br N O4 S
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER



**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

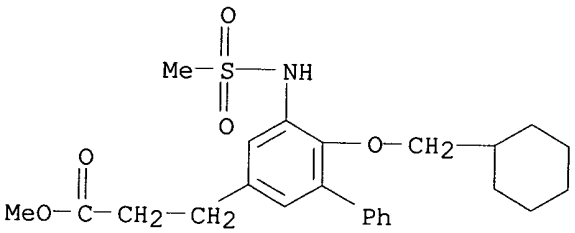
L7 ANSWER 3 OF 8 REGISTRY COPYRIGHT 2002 ACS
RN 222628-45-7 REGISTRY
CN **[1,1'-Biphenyl]-3-propanoic acid, 6-(cyclohexylmethoxy)-5-[[(dimethylamino)sulfonyl]amino]-, methyl ester (9CI)** (CA INDEX NAME)
OTHER NAMES:
CN **3-(2-(Cyclohexylmethoxy)-3-((dimethylsulfamoyl)amino)-1,1'-biphenyl-5-yl)propionic acid methyl ester**
FS 3D CONCORD
MF C25 H34 N2 O5 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL



**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

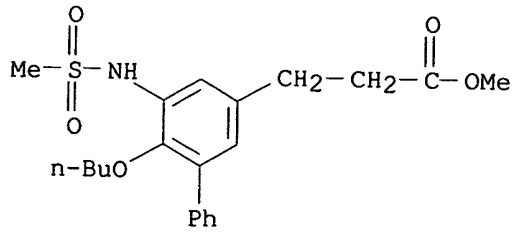
L7 ANSWER 4 OF 8 REGISTRY COPYRIGHT 2002 ACS
RN 222628-42-4 REGISTRY
CN **[1,1'-Biphenyl]-3-propanoic acid, 6-(cyclohexylmethoxy)-5-[(methylsulfonyl)amino]-, methyl ester (9CI)** (CA INDEX NAME)
OTHER NAMES:
CN **3-(2-(Cyclohexylmethoxy)-3-((methylsulfonyl)amino)-1,1'-biphenyl-5-yl)propionic acid methyl ester**
FS 3D CONCORD
MF C24 H31 N O5 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL



**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

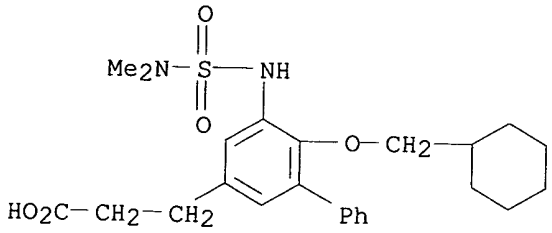
L7 ANSWER 5 OF 8 REGISTRY COPYRIGHT 2002 ACS
RN 222628-38-8 REGISTRY
CN **[1,1'-Biphenyl]-3-propanoic acid, 6-butoxy-5-[(methylsulfonyl)amino]-, methyl ester (9CI)** (CA INDEX NAME)
OTHER NAMES:
CN **3-(2-Butoxy-3-((methylsulfonyl)amino)-1,1'-biphenyl-5-yl)propionic acid methyl ester**
FS 3D CONCORD
MF C21 H27 N O5 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL



**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

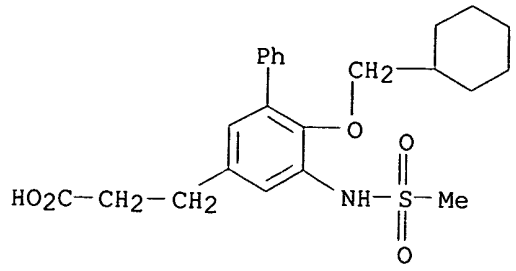
L7 ANSWER 6 OF 8 REGISTRY COPYRIGHT 2002 ACS
RN 222627-13-6 REGISTRY
CN **[1,1'-Biphenyl]-3-propanoic acid, 6-(cyclohexylmethoxy)-5-[[(dimethylamino)sulfonyl]amino]- (9CI)** (CA INDEX NAME)
OTHER NAMES:
CN **3-(2-(Cyclohexylmethoxy)-3-((dimethylsulfamoyl)amino)-1,1'-biphenyl-5-yl)propionic acid**
FS 3D CONCORD
MF C24 H32 N2 O5 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL



**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

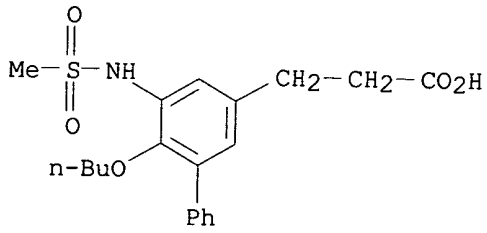
L7 ANSWER 7 OF 8 REGISTRY COPYRIGHT 2002 ACS
RN 222627-10-3 REGISTRY
CN **[1,1'-Biphenyl]-3-propanoic acid, 6-(cyclohexylmethoxy)-5-[(methylsulfonyl)amino]- (9CI)** (CA INDEX NAME)
OTHER NAMES:
CN **3-(2-(Cyclohexylmethoxy)-3-((methylsulfonyl)amino)-1,1'-biphenyl-5-yl)propionic acid**
FS 3D CONCORD
MF C23 H29 N O5 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL




**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L7 ANSWER 8 OF 8 REGISTRY COPYRIGHT 2002 ACS
RN 222627-07-8 REGISTRY
CN **[1,1'-Biphenyl]-3-propanoic acid, 6-butoxy-5-[(methylsulfonyl)amino]-(9CI)** (CA INDEX NAME)
OTHER NAMES:
CN **3-(2-Butoxy-3-((methylsulfonyl)amino)-1,1'-biphenyl-5-yl)propionic acid**
FS 3D CONCORD
MF C20 H25 N O5 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL



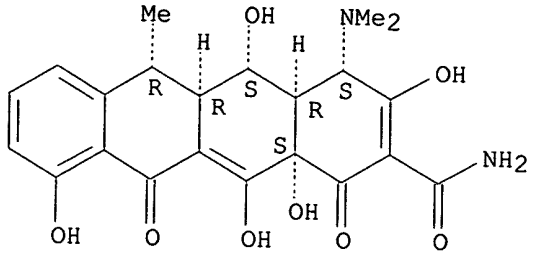

**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

```
=> s doyxcycline/cn
L10             0 DOYXCYCLINE/CN

=> s doxycycline
L11            34 DOXYCYCLINE

=> s doxycycline/cn
L12             1 DOXYCYCLINE/CN

=> d

L12  ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2002 ACS
```

RN 564-25-0 REGISTRY
CN 2-Naphthacenecarboxamide,
4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-
3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-, (4S,4aR,5S,5aR,6R,12aS)-
(9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 2-Naphthacenecarboxamide,
4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-
3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo- (6CI, 8CI)
CN 2-Naphthacenecarboxamide,
4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-
3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-, [4S-
(4.alpha.,4a.alpha.,5.alpha.,5a.alpha.,6.alpha.,12a.alpha.)]-
OTHER NAMES:
CN .alpha.-6-Deoxy-5-hydroxytetracycline
CN .alpha.-6-Deoxyoxytetracycline
CN .alpha.-Doxycycline
CN 4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-
pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide
CN 5-Hydroxy-.alpha.-6-deoxytetracycline
CN 6-Deoxy-5-hydroxytetracycline
CN 6-Deoxyoxytetracycline
CN Deoxymykoin
CN Doxivetin
CN Doxycen
CN **Doxycycline**
CN Doxytetracycline
CN GS 3065
CN Hydramycin
CN Liviatin
CN Monodox
CN Oxytetracycline, 6-deoxy-
CN Ronaxan
CN Vibramycin
CN Vibramycine
CN Vibravenos
FS STEREOSEARCH
DR 7164-70-7, 7264-10-0, 10597-92-9
MF C22 H24 N2 O8
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*,
BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS,
CASREACT, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, CSNB, DDFU,
DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, HSDB*, IFICDB,
IFIPAT, IFIUDB, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC, PHAR,
PHARMASEARCH, PROMT, RTECS*, SPECINFO, TOXCENTER, USAN, USPAT2,
USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)

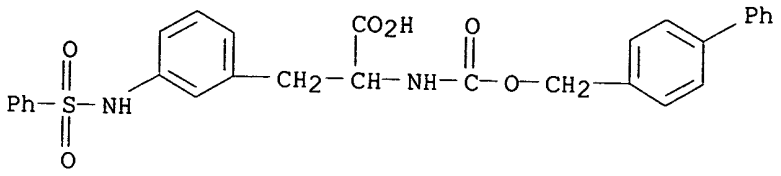
Absolute stereochemistry.




**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

2640 REFERENCES IN FILE CA (1967 TO DATE)
39 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
2643 REFERENCES IN FILE CAPLUS (1967 TO DATE)
6 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

```
=> s propionic acid and amin?
         28006 PROPIONIC
       5473436 ACID
          7807 ACIDS
       5479119 ACID
                 (ACID OR ACIDS)
         27829 PROPIONIC ACID
                 (PROPIONIC(W)ACID)
       4948784 AMIN?
L13       4267 PROPIONIC ACID AND AMIN?

=> s l13 and biphenyl
        283086 BIPHENYL
L14         75 L13 AND BIPHENYL

=> s sulfonyl or sulphonyl
        740670 SULFONYL
             1 SULFONYLS
        740670 SULFONYL
                 (SULFONYL OR SULFONYLS)
            90 SULPHONYL
L15     740690 SULFONYL OR SULPHONYL

=> s l14 and l15
L16          8 L14 AND L15

=> d l16

L16  ANSWER 1 OF 8  REGISTRY  COPYRIGHT 2002 ACS
RN   361457-69-4  REGISTRY
CN   Phenylalanine, N-[([1,1'-biphenyl]-4-ylmethoxy)carbonyl]-3-
     [(phenylsulfonyl)amino]- (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   3-(3-Benzenesulfonylaminophenyl)-2-(biphenyl-4-
     ylmethoxycarbonylamino)propionic acid
FS   3D CONCORD
MF   C29 H26 N2 O6 S
SR   CA
LC   STN Files:   CA, CAPLUS, USPATFULL
```



**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

```
=> s propionic acid and 3-phenyl
         28006 PROPIONIC
       5473436 ACID
          7807 ACIDS
       5479119 ACID
                 (ACID OR ACIDS)
         27829 PROPIONIC ACID
                 (PROPIONIC(W)ACID)
      10978192 3
       8015767 PHENYL
            14 PHENYLS
       8015767 PHENYL
                 (PHENYL OR PHENYLS)
        385118 3-PHENYL
                 (3(W)PHENYL)
L17        621 PROPIONIC ACID AND 3-PHENYL

=> s amino
       3710800 AMINO
          8625 AMINOS
SYSTEM LIMITS EXCEEDED - SEARCH ENDED
The search profile you entered was too complex or gave too many
answers.  Simplify or subdivide the query and try again.  If you have
exceeded the answer limit, enter DELETE HISTORY at an arrow prompt
(=>) to remove all previous answers sets and begin at L1.  Use the
SAVE command to store any important profiles or answer sets before
using DELETE HISTORY.

=> s l17 and amin?
       4948784 AMIN?
L18        152 L17 AND AMIN?

=> s phenyl and l18
       8015767 PHENYL
            14 PHENYLS
       8015767 PHENYL
                 (PHENYL OR PHENYLS)
L19        152 PHENYL AND L18

=> s sulfonyl
        740670 SULFONYL
             1 SULFONYLS
L20     740670 SULFONYL
```

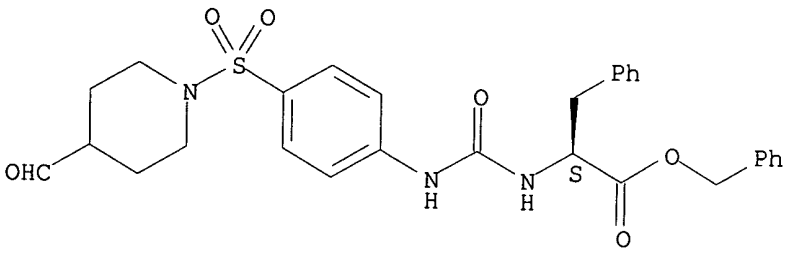
(SULFONYL OR SULFONYLS)
75% OF LIMIT FOR TOTAL ANSWERS REACHED

=> s l19 and sulfonyl
740670 SULFONYL
1 SULFONYLS
740670 SULFONYL
(SULFONYL OR SULFONYLS)
L21 17 L19 AND SULFONYL

=> d l21 1-17

L21 ANSWER 1 OF 17 REGISTRY COPYRIGHT 2002 ACS
RN 392692-16-9 REGISTRY
CN **L-Phenylalanine, N-[[[4-[(4-formyl-1-piperidinyl)sulfonyl]phenyl]amino]carbonyl]-, phenylmethyl ester (9CI)** (CA INDEX NAME)
OTHER NAMES:
CN **(2S)-2-[3-[4-(4-Formylpiperidine-1-sulfonyl)phenyl]ureido]-3-phenylpropionic acid benzyl ester**
FS STEREOSEARCH
MF C29 H31 N3 O6 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.

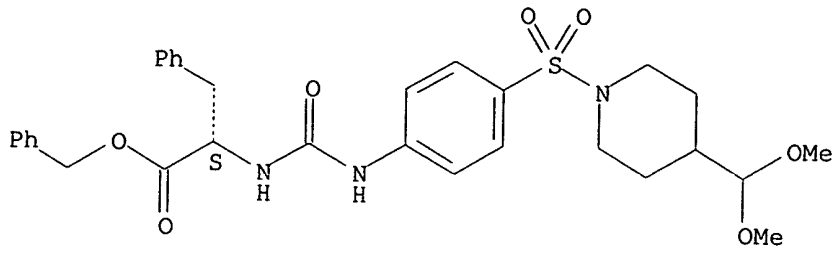


**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L21 ANSWER 2 OF 17 REGISTRY COPYRIGHT 2002 ACS
RN 392692-15-8 REGISTRY
CN **L-Phenylalanine, N-[[[4-[[4-(dimethoxymethyl)-1-piperidinyl]sulfonyl]phenyl]amino]carbonyl]-, phenylmethyl ester (9CI)** (CA INDEX NAME)
OTHER NAMES:
CN **(2S)-2-[3-[4-(4-Dimethoxymethylpiperidine-1-sulfonyl)phenyl]ureido]-3-phenylpropionic acid benzyl ester**
FS STEREOSEARCH
MF C31 H37 N3 O7 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.

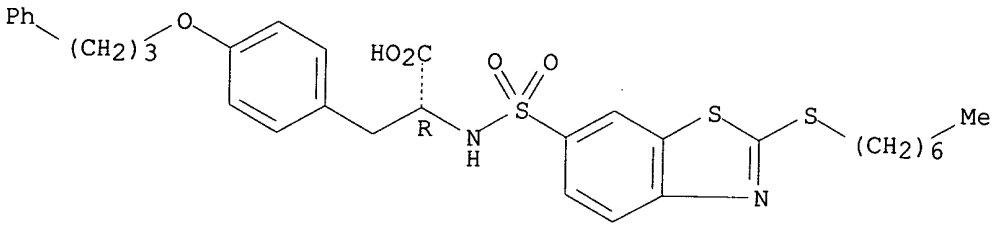


**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L21 ANSWER 3 OF 17 REGISTRY COPYRIGHT 2002 ACS
RN 367517-36-0 REGISTRY
CN **D-Tyrosine, N-[[2-(heptylthio)-6-benzothiazolyl]sulfonyl]-O-(3-phenylpropyl)- (9CI)** (CA INDEX NAME)
OTHER NAMES:
CN **(2R)-2-[(2-Heptylthiobenzothiazole-6-sulfonyl)amino]-3-[4-(3-phenylpropyl)oxyphenyl]propionic acid**
FS STEREOSEARCH
MF C32 H38 N2 O5 S3
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

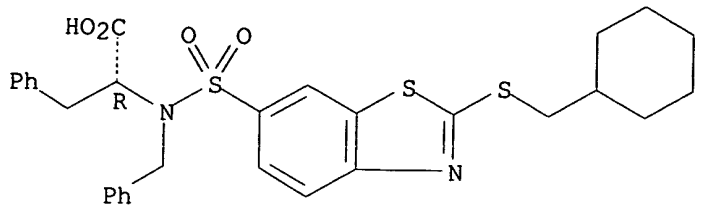


**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L21 ANSWER 4 OF 17 REGISTRY COPYRIGHT 2002 ACS
RN 367516-82-3 REGISTRY
CN **D-Phenylalanine, N-[[2-[(cyclohexylmethyl)thio]-6-benzothiazolyl]sulfonyl]-N-(phenylmethyl)- (9CI)** (CA INDEX NAME)
OTHER NAMES:
CN **(2R)-2-[[2-(Cyclohexylmethylthio)benzothiazole-6-sulfonyl]benzylamino]-3-phenylpropionic acid**
FS STEREOSEARCH
MF C30 H32 N2 O4 S3
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

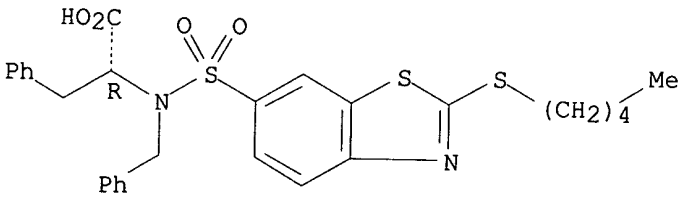


**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L21 ANSWER 5 OF 17 REGISTRY COPYRIGHT 2002 ACS
RN 367516-81-2 REGISTRY
CN **D-Phenylalanine, N-[[2-(pentylthio)-6-benzothiazolyl]sulfonyl]-N-(phenylmethyl)- (9CI)** (CA INDEX NAME)
OTHER NAMES:
CN **(2R)-2-[(2-Pentylthiobenzothiazole-6-sulfonyl)benzylamino]-3-phenylpropionic acid**
FS STEREOSEARCH
MF C28 H30 N2 O4 S3
SR CA
LC STN Files: CA, CAPLUS

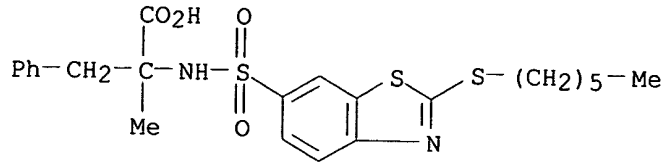
Absolute stereochemistry.



**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L21 ANSWER 6 OF 17 REGISTRY COPYRIGHT 2002 ACS
RN 367516-66-3 REGISTRY
CN **Phenylalanine, N-[[2-(hexylthio)-6-benzothiazolyl]sulfonyl]-.alpha.-methyl- (9CI)** (CA INDEX NAME)
OTHER NAMES:
CN **(.+-.)-2-[(2-Hexylthiobenzothiazole-6-sulfonyl)amino]-2-methyl-3-phenylpropionic acid**
MF C23 H28 N2 O4 S3
SR CA
LC STN Files: CA, CAPLUS

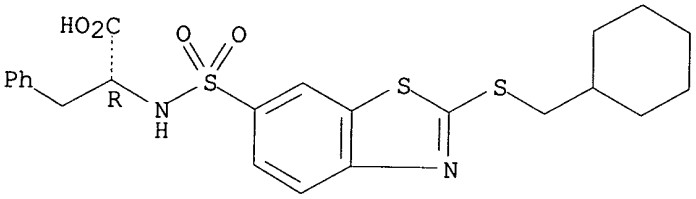


**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L21 ANSWER 7 OF 17 REGISTRY COPYRIGHT 2002 ACS
RN 367516-52-7 REGISTRY
CN **D-Phenylalanine, N-[[2-[(cyclohexylmethyl)thio]-6-benzothiazolyl]sulfonyl]- (9CI)** (CA INDEX NAME)
OTHER NAMES:
CN **(2R)-2-[[2-(Cyclohexylmethylthio)benzothiazole-6-sulfonyl]amino]-3-phenylpropionic acid**
FS STEREOSEARCH
MF C23 H26 N2 O4 S3
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

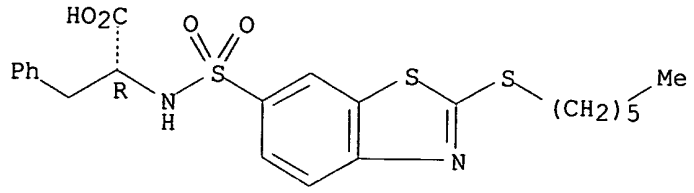


**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L21 ANSWER 8 OF 17 REGISTRY COPYRIGHT 2002 ACS
RN 367516-51-6 REGISTRY
CN **D-Phenylalanine, N-[[2-(hexylthio)-6-benzothiazolyl]sulfonyl]- (9CI)** (CA INDEX NAME)
OTHER NAMES:
CN **(2R)-2-[(2-Hexylthiobenzothiazole-6-sulfonyl)amino]-3-phenylpropionic acid**
FS STEREOSEARCH
MF C22 H26 N2 O4 S3
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

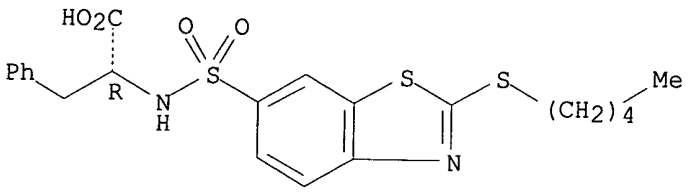


**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L21 ANSWER 9 OF 17 REGISTRY COPYRIGHT 2002 ACS
RN 367516-49-2 REGISTRY
CN **D-Phenylalanine, N-[[2-(pentylthio)-6-benzothiazolyl]sulfonyl]-(9CI)** (CA INDEX NAME)
OTHER NAMES:
CN **(2R)-2-[(2-Pentylthiobenzothiazole-6-sulfonyl)amino]-3-phenylpropionic acid**
FS STEREOSEARCH
MF C21 H24 N2 O4 S3
SR CA
LC STN Files: CA, CAPLUS

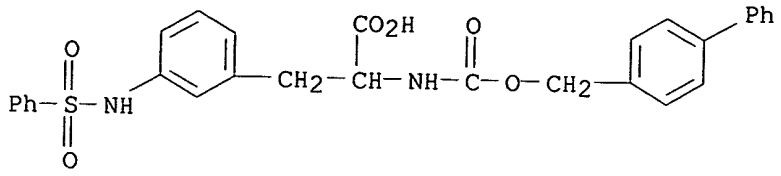
Absolute stereochemistry.



**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L21 ANSWER 10 OF 17 REGISTRY COPYRIGHT 2002 ACS
RN 361457-69-4 REGISTRY
CN **Phenylalanine, N-[([1,1'-biphenyl]-4-ylmethoxy)carbonyl]-3-[(phenylsulfonyl)amino]- (9CI)** (CA INDEX NAME)
OTHER NAMES:
CN **3-(3-Benzenesulfonylaminophenyl)-2-(biphenyl-4-ylmethoxycarbonylamino)propionic acid**
FS 3D CONCORD
MF C29 H26 N2 O6 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

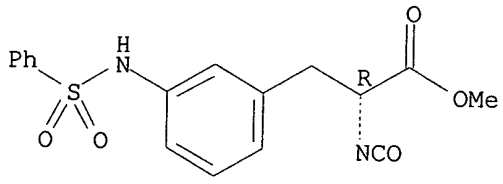


**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L21 ANSWER 11 OF 17 REGISTRY COPYRIGHT 2002 ACS
RN 361456-48-6 REGISTRY
CN **Benzenepropanoic acid, .alpha.-isocyanato-3-[(phenylsulfonyl)amino]-, methyl ester, (.alpha.R)- (9CI)** (CA INDEX NAME)
OTHER NAMES:
CN **(R)-2-Isocyanato-3-(3-benzenesulfonylaminophenyl)propionic acid methyl ester**
FS STEREOSEARCH
MF C17 H16 N2 O5 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.

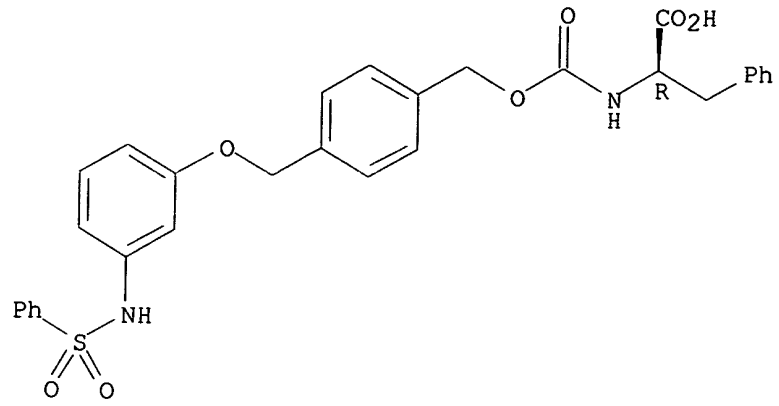


**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L21 ANSWER 12 OF 17 REGISTRY COPYRIGHT 2002 ACS
RN 361456-41-9 REGISTRY
CN **D-Phenylalanine, N-[[[4-[[3-[(phenylsulfonyl)amino]phenoxy]methyl]phenyl]methoxy]carbonyl]- (9CI)** (CA INDEX NAME)
OTHER NAMES:
CN **(R)-2-[4-(3-Benzenesulfonylaminophenoxymethyl)benzyloxycarbonylamino]-3-phenylpropionic acid**
FS STEREOSEARCH
MF C30 H28 N2 O7 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.

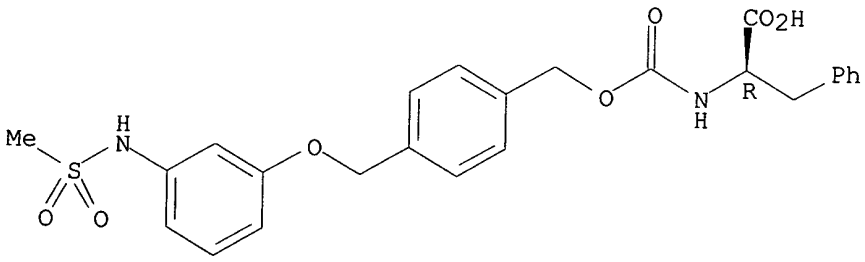


**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L21 ANSWER 13 OF 17 REGISTRY COPYRIGHT 2002 ACS
RN 361456-40-8 REGISTRY
CN **D-Phenylalanine, N-[[[4-[[3-[(methylsulfonyl)amino]phenoxy]methyl]phenyl]methoxy]carbonyl]- (9CI)** (CA INDEX NAME)
OTHER NAMES:
CN **(R)-2-[4-(3-Methanesulfonylaminophenoxymethyl)benzyloxycarbonylamino]-3-phenylpropionic acid**
FS STEREOSEARCH
MF C25 H26 N2 O7 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.

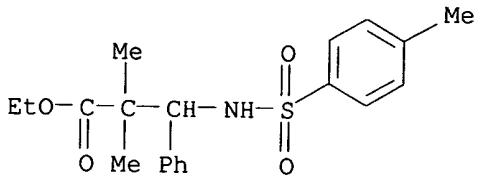


**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L21 ANSWER 14 OF 17 REGISTRY COPYRIGHT 2002 ACS
RN 329363-56-6 REGISTRY
CN **Benzenepropanoic acid, .alpha.,.alpha.-dimethyl-.beta.-[[(4-methylphenyl)sulfonyl]amino]-, ethyl ester (9CI)** (CA INDEX NAME)
OTHER NAMES:

CN **2,2-Dimethyl-3-phenyl-3-(toluene-4-sulfonylamino)propionic Acid Ethyl Ester**
FS 3D CONCORD
MF C20 H25 N O4 S
SR CA
LC STN Files: CA, CAPLUS, CASREACT

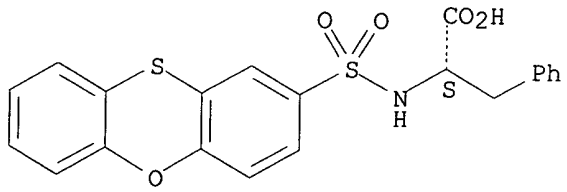


**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L21 ANSWER 15 OF 17 REGISTRY COPYRIGHT 2002 ACS
RN 292050-59-0 REGISTRY
CN **L-Phenylalanine, N-(2-phenoxathiinylsulfonyl)- (9CI)** (CA INDEX NAME)
OTHER NAMES:
CN **(S)-2-(Phenoxathiin-2-ylsulfonylamino)-3-phenylpropionic acid**
FS STEREOSEARCH
MF C21 H17 N O5 S2
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Absolute stereochemistry.



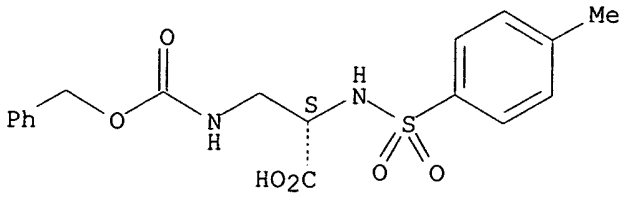
**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L21 ANSWER 16 OF 17 REGISTRY COPYRIGHT 2002 ACS
RN 28415-52-3 REGISTRY
CN **L-Alanine, N-[(4-methylphenyl)sulfonyl]-3-[[(phenylmethoxy)carbonyl]amino]- (9CI)** (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN **Propionic acid, 3-(carboxyamino)-2-p-toluenesulfonamido-, N-benzyl ester, L- (8CI)**
FS STEREOSEARCH
MF C18 H20 N2 O6 S

CI COM
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

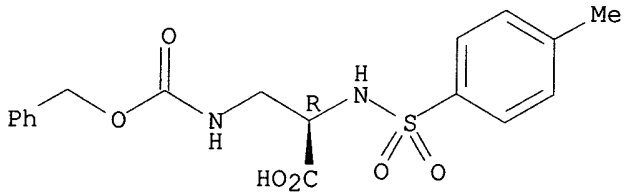


**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L21 ANSWER 17 OF 17 REGISTRY COPYRIGHT 2002 ACS
RN 28415-51-2 REGISTRY
CN **D-Alanine, N-[(4-methylphenyl)sulfonyl]-3-[[(phenylmethoxy)carbonyl]amino]- (9CI)** (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN **Propionic acid, 3-(carboxyamino)-2-p-toluenesulfonamido-, N-benzyl ester, D- (8CI)**
FS STEREOSEARCH
MF C18 H20 N2 O6 S
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

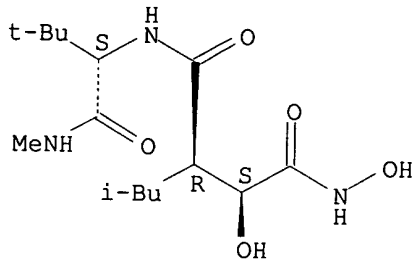
=> s marimastat/cn
L22 1 MARIMASTAT/CN

=> d

L22 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS
RN 154039-60-8 REGISTRY
CN Butanediamide, N4-[(1S)-2,2-dimethyl-1-[(methylamino)carbonyl]propyl]-N1,2-dihydroxy-3-(2-methylpropyl)-, (2S,3R)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:

CN Butanediamide, N4-[2,2-dimethyl-1-[(methylamino)carbonyl]propyl]-N1,2-dihydroxy-3-(2-methylpropyl)-, [2S-[N4(R*),2R*,3S*]]-
OTHER NAMES:
CN BB 2516
CN **Marimastat**
FS STEREOSEARCH
MF C15 H29 N3 O5
SR CAS Registry Services
LC STN Files: ADISINSIGHT, ADISNEWS, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CIN, CSCHEM, DDFU, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, PHAR, PROMT, SYNTHLINE, TOXCENTER, USAN, USPATFULL
Other Sources: WHO

Absolute stereochemistry.




**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

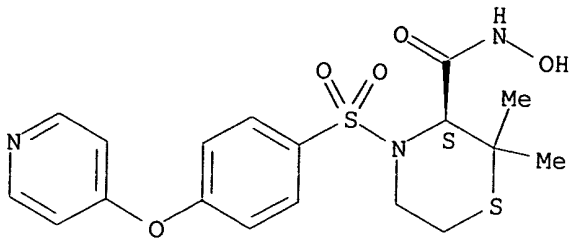
84 REFERENCES IN FILE CA (1967 TO DATE)
5 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
84 REFERENCES IN FILE CAPLUS (1967 TO DATE)

=> s prinomastat/cn
L23 1 PRINOMASTAT/CN

=> d

L23 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS
RN 192329-42-3 REGISTRY
CN 3-Thiomorpholinecarboxamide, N-hydroxy-2,2-dimethyl-4-[[4-(4-pyridinyloxy)phenyl]sulfonyl]-, (3S)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 3-Thiomorpholinecarboxamide, N-hydroxy-2,2-dimethyl-4-[[4-(4-pyridinyloxy)phenyl]sulfonyl]-, (S)-
OTHER NAMES:
CN AG 3340
CN **Prinomastat**
FS STEREOSEARCH
DR 195008-93-6
MF C18 H21 N3 O5 S2
SR CA
LC STN Files: ADISINSIGHT, BIOSIS, BIOTECHNO, CA, CAPLUS, DRUGNL, DRUGPAT, DRUGUPDATES, EMBASE, IPA, SYNTHLINE, TOXCENTER, USPATFULL

Absolute stereochemistry.



**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

33 REFERENCES IN FILE CA (1967 TO DATE)
33 REFERENCES IN FILE CAPLUS (1967 TO DATE)

=> s RS 130/cn
L24 1 RS 130/CN

=> d

L24 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS
RN 12633-21-5 REGISTRY
CN Titanium alloy, base, Ti 89-94,Al 3.0-5.0,Mn 3.0-5.0,FE 0-0.50,O 0-0.20,C 0-0.15,N 0-0.07,H 0-0.0125 (UNS R56440) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Aluminum 4, manganese 4, titanium 92
CN AMS 4925
CN C130AM
CN Hylite 40
CN IMI 314
CN IMI.314A
CN **RS 130**
CN T-A4M
CN Ti4Al4Mn
CN UNS R56440
AR 39348-05-5
DR 12617-16-2, 51570-08-2
MF C . Al . Fe . H . Mn . N . O . Ti
CI AYS
LC STN Files: ASMDATA*, CA, CAPLUS, USPATFULL
(*File contains numerically searchable property data)

| Component | Component Percent | Component Registry Number |
|---|---|---|
| Ti | 89 - 94 | 7440-32-6 |
| Al | 3.0 - 5.0 | 7429-90-5 |
| Mn | 3.0 - 5.0 | 7439-96-5 |
| Fe | 0 - 0.50 | 7439-89-6 |
| O | 0 - 0.20 | 17778-80-2 |
| C | 0 - 0.15 | 7440-44-0 |
| N | 0 - 0.07 | 17778-88-0 |
| H | 0 - 0.0125 | 12385-13-6 |

22 REFERENCES IN FILE CA (1967 TO DATE)
22 REFERENCES IN FILE CAPLUS (1967 TO DATE)

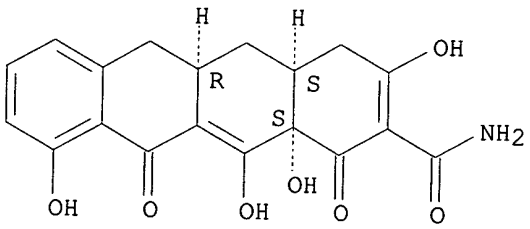
=> s metasta/cn
L25 0 METASTA/CN

=> s metastat/cn
L26 1 METASTAT/CN

=> d

L26 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS
RN 15866-90-7 REGISTRY
CN 2-Naphthacenecarboxamide, 1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-, (4aS,5aR,12aS)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 2-Naphthacenecarboxamide, 1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-, [4aS-(4a.alpha.,5a.alpha.,12a.alpha.)]-
CN 2-Naphthacenecarboxamide, 1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo- (7CI, 8CI)
OTHER NAMES:
CN 4-De(dimethylamino)-6-demethyl-6-deoxytetracycline
CN 4-De(dimethylamino)sancycline
CN CMT 3
CN COL 3
CN **Metastat**
FS STEREOSEARCH
DR 15867-23-9
MF C19 H17 N O7
LC STN Files: ADISNEWS, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CAOLD, CAPLUS, CIN, DRUGNL, DRUGUPDATES, EMBASE, PHAR, PROMT, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry.




**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

63 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
63 REFERENCES IN FILE CAPLUS (1967 TO DATE)
4 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=> s periostat/cn
L27 0 PERIOSTAT/CN

=> s neovastat/cn
L28 1 NEOVASTAT/CN

=> d

L28 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS
RN 305838-77-1 REGISTRY
CN **Neovastat (9CI)** (CA INDEX NAME)
OTHER NAMES:
CN AE 941
DR 360069-52-9
MF Unspecified
CI MAN
SR CA
LC STN Files: BIOSIS, CA, CAPLUS, TOXCENTER

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
4 REFERENCES IN FILE CA (1967 TO DATE)
4 REFERENCES IN FILE CAPLUS (1967 TO DATE)

=> file embase biosis medline caplus uspatfull
COST IN U.S. DOLLARS

| | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| FULL ESTIMATED COST | 184.82 | 185.03 |

FILE 'EMBASE' ENTERED AT 17:31:01 ON 09 JUL 2002
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FILE 'BIOSIS' ENTERED AT 17:31:01 ON 09 JUL 2002
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FILE 'MEDLINE' ENTERED AT 17:31:01 ON 09 JUL 2002

FILE 'CAPLUS' ENTERED AT 17:31:01 ON 09 JUL 2002
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PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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FILE 'USPATFULL' ENTERED AT 17:31:01 ON 09 JUL 2002
CA INDEXING COPYRIGHT (C) 2002 AMERICAN CHEMICAL SOCIETY (ACS)

=> s doxycycline or 15039-60-8/rn
'RN' IS NOT A VALID FIELD CODE
'RN' IS NOT A VALID FIELD CODE
'RN' IS NOT A VALID FIELD CODE
L29 26760 DOXYCYCLINE OR 15039-60-8/RN

=> s sinusoidal obstruction syndrome or SOS or hepatic venoocclusive disease
L30 16748 SINUSOIDAL OBSTRUCTION SYNDROME OR SOS OR HEPATIC VENOOCCLUSIVE
DISEASE

=> s l30 and l29
L31 7 L30 AND L29

=> s l31 and py<2001
2 FILES SEARCHED...
L32 4 L31 AND PY<2001

=> d l32 1-4 ab bib kwic

L32 ANSWER 1 OF 4 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

AB Toxin synthesis by Shiga toxin-producing Escherichia coli (STEC) appears to be coregulated through induction of the integrated bacteriophage that encodes the toxin gene. Phage production is linked to induction of the bacterial **SOS** response, a ubiquitous response to DNA damage. **SOS**-inducing antimicrobial agents, particularly the quinolones, trimethoprim, and furazolidone, were shown to induce toxin gene expression in studies of their effects on a reporter STEC strain carrying a chromosome-based stx2::lacZ transcriptional fusion. At antimicrobial levels above those required to inhibit bacterial replication, these agents are potent inducers (up to 140-fold) of the transcription of type 2 Shiga toxin genes (stx2); therefore, they should be avoided in treating patients with potential or confirmed STEC infections. Other agents (20 studied) and incubation conditions produced significant but less striking effects on stx2 transcription; positive and negative influences were observed. **SOS**-mediated induction of toxin synthesis also provides a mechanism that could exacerbate STEC infections and increase dissemination of stx genes. These features and the use of **SOS**-inducing antibiotics in clinical practice and animal husbandry may account for the recent emergence of STEC disease.

AN 2000371056 EMBASE

TI Toxin gene expression by Shiga toxin-producing Escherichia coli: The role of antibiotics and the bacterial **SOS** response.

AU Kimmitt P.T.; Harwood C.R.; Barer M.R.

CS M.R. Barer, Dept. of Microbiology and Immunology, University of Newcastle, Medical School, Framlington Place, Newcastle upon Tyne NE2 4HH, United Kingdom. m.r.barer@ncl.ac.uk

SO Emerging Infectious Diseases, (2000) 6/5 (458-465).
Refs: 32
ISSN: 1080-6040 CODEN: EIDIFA

CY United States

DT Journal; Article

FS 004 Microbiology
037 Drug Literature Index
052 Toxicology

LA English

SL English

TI Toxin gene expression by Shiga toxin-producing Escherichia coli: The role of antibiotics and the bacterial **SOS** response.

SO Emerging Infectious Diseases, (2000) 6/5 (458-465).
Refs: 32
ISSN: 1080-6040 CODEN: EIDIFA

AB . . . through induction of the integrated bacteriophage that encodes the toxin gene. Phage production is linked to induction of the bacterial **SOS** response, a ubiquitous response to DNA damage. **SOS**-inducing antimicrobial agents, particularly the quinolones, trimethoprim, and furazolidone, were shown to induce toxin gene expression in studies of their effects. . . (20 studied) and incubation conditions produced significant but less striking effects on stx2 transcription; positive and negative influences were observed. **SOS**-mediated induction of toxin synthesis also provides a mechanism that could exacerbate STEC infections and increase dissemination of stx genes. These features and the

use of **SOS**-inducing antibiotics in clinical practice and animal husbandry may account for the recent emergence of STEC disease.

CT Medical Descriptors:
*gene expression
*Escherichia coli
***SOS chromotest**
toxin synthesis
bacteriophage
DNA damage
gene induction
genetic transcription
Enterobacter infection
disease exacerbation
reporter gene
nonhuman
article
*Shiga toxin
*antibiotic agent
quinoline derived antiinfective agent
trimethoprim
furazolidone
novobiocin
metronidazole
cefalexin
amoxicillin
amoxicillin plus clavulanic acid
ampicillin
piperacillin plus tazobactam
imipenem
aztreonam
cefuroxime
ceftazidime
cefotaxime
fosfomycin
polymyxin B
gentamicin
chloramphenicol
**doxycycline**
erythromycin
rifampicin

RN. . . 56238-63-2; (ceftazidime) 72558-82-8; (cefotaxime) 63527-52-6, 64485-93-4; (fosfomycin) 23155-02-4; (polymyxin B) 1404-26-8, 1405-20-5; (gentamicin) 1392-48-9, 1403-66-3, 1405-41-0; (chloramphenicol) 134-90-7, 2787-09-9, 56-75-7; (**doxycycline**) 10592-13-9, 17086-28-1, 564-25-0; (erythromycin) 114-07-8, 70536-18-4; (rifampicin) 13292-46-1

L32 ANSWER 2 OF 4 USPATFULL

AB It has been found that sugar acid salts represent beneficial controlled release forms for basic organic drug compounds. Examples of appropriate salts include mono, di, oligo and polysaccharide poly-O-sulphonic acid salts of antibiotics such as tetracyclins and aminoglycosides.

AN 2000:77338 USPATFULL

TI Drug salts

IN Dyrsting, Hjarne, Virum, Denmark
Koch, Torben, Copenhagen, Denmark

PA Dumex-Alpharma A/S, Copenhagen, Denmark (non-U.S. corporation)

PI US 6077822 20000620 <--

AI US 1995-402619 19950313 (8)

RLI Continuation-in-part of Ser. No. US 1993-141625, filed on 27 Oct 1993, now patented, Pat. No. US 5595977 And a continuation-in-part of Ser. No.

US 1994-265193, filed on 24 Jun 1994, now patented, Pat. No. US 5538954
And a continuation-in-part of Ser. No. WO 1994-DK341, filed on 13 Sep 1994

PRAI DK 1993-1034 19930914
DK 1994-667 19940610

DT Utility

FS Granted

EXNAM Primary Examiner: Peselev, Elli

LREP Watov & Kipnes, P.C.

CLMN Number of Claims: 19

ECL Exemplary Claim: 17

DRWN 3 Drawing Figure(s); 3 Drawing Page(s)

LN.CNT 1639

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 6077822 20000620 <--

SUMM The disaccharide sulphonic acids are especially preferred, in particular the sucrose sulphonic acids such as sucrose-octa-O-sulphonic acid ( **SOS**).

DRWD FIG. 1 is a plot of dissolution rate for doxycyclin.**SOS** salt according to the invention compared with the commercial product Vibramycin,

DETD . . . the present invention is the sulphate octa-ester of sucrose, .beta.-D-fructofuranosyl-.alpha.-D-glucopyranoside octakis (hydrogen sulphate), hereinafter referred to as sucrose-octa-O-sulphonic acid or **SOS**.

DETD **SOS** may be prepared by sulphating sucrose with sulphur trioxide in pyridine. **SOS** forms crystalline, water soluble sodium, potassium, caesium, rubidium and ammonium salts as reported by Ochi (supra).

DETD **SOS** also forms an aluminum salt, C.sub.12 H.sub.54 Al.sub.16 O.sub.75 S.sub.8, which is known as sucralfate. This aluminum salt may be prepared by reaction of **SOS** with aluminum hydroxide (see U.S. Pat. No. 3,432,489 (Chugai)) and is widely used for the treatment of gastric ulcers, its. . .

DETD By way of example the aminoglycoside **SOS** salts can be represented by the formula

DETD The salts with **SOS** are crystalline and particularly preferred. These can be described by the following formula:

DETD By way of example, a soluble aminoglycoside (e.g. kanamycin A) may be dissolved in water and a solution of **SOS** may be added thereto. The drug:sugar acid salt separates out as a syrup which can be crystallized from ethanol.

DETD . . . example, to a solution of a tetracyclin (e.g. doxycyclin) in hydrochloric acid there may be added an aqueous solution of **SOS** -sodium salt. The drug:sugar acid salt precipitates out.

DETD Doxycyclin **SOS** Salt

DETD Doxycyclin **SOS** Salt

DETD Doxycyclin **SOS** Salt

DETD . . . in 300 ml water, with 18.5 g (40 mmol) doxycylin monohydrate dissolved in 400 ml 0.1 M HCl, precipitation of **doxycycline** sucrose octasulphate takes place. The reaction mixture is stirred for about 60 min at 25.degree. C., filtered, washed with 3.times.50. . .

DETD In a first experiment, the tobrymycin-**SOS** salt from Example 12 containing 44% tobramycin, was tested. As a reference, a physical mixture of sucralfate 56%/tobramycin 44% was. . .

DETD

| Test Substance | Buffer a. pH 2.0 |
|---|---|
| | Buffer b. pH 7.4 |

| | | |
|---|---|---|
| **SOS**-tobramycin salt from Example 12 | 59% | 31% |
| **SOS**/tobramycin physical mixture 56:44 | 8% | 1% |

| DETD Test Substance | Buffer a. pH 2.0 | Buffer b. pH 7.4 |
|---|---|---|
| **SOS**-Al-tobramycin salt from Example 16 | 61% | 65% |
| Sucralfate 94.4%-tobramycin 5.6% physical mixture | 40% | 50% |

DETD Bacitracin-**SOS**:
DETD Cyclobenzaprine-**SOS**:
DETD Diltiazem-**SOS**:
DETD Erythromycin-**SOS**:
DETD Nortriptyline-**SOS**:
DETD Noscapine-**SOS**:
DETD Polymyxin-**SOS**:
DETD Quinidine-**SOS**:
DETD Vancomycin-**SOS**:
DETD Verapamil-**SOS**:

L32 ANSWER 3 OF 4 USPATFULL
AB A method for detecting a tetracycline efflux pump inhibitor in the presence of tetracycline using a reporter gene system where the tetA promoter directs transcription of a reporter gene (lacZ) while the tetA is under the control of the tet repressor encoded by the tetR gene is described. The method uses a cell having a reporter gene system where the tetA promoter directs transcription of a reporter gene (lacZ) and an active efflux system in which relatively modest levels of the efflux protein encoded by the tetA gene are produced in a constitutive manner, i.e., not under the control of the tet repressor encoded by the tetR gene. Test samples which are inhibitors of the TetA efflux protein will allow accumulation of tetracycline inside the cells at levels which will induce expression of the tetA-lacZ transcriptional fusion to give a positive signal. A microorganism is also described which is refractory to induction by DNA damaging agents and comprises (1) an indicator gene fused to a tetA promoter, as a single- or low-copy number gene; (2) a tetR gene expressed at low levels, preferably at a level producing a sensitivity to 10 ng or less of tetracycline, and (3) a constitutive gene encoding a tetracycline efflux pump.
AN 1998:91819 USPATFULL
TI Tetracycline-efflux pump inhibitor screening methods
IN Rothstein, David Michael, Pomona, NY, United States
Guay, Gordon Gerald, Harriman, NY, United States
PA American Cyanamid Company, Madison, NJ, United States (U.S. corporation)
PI US 5789188 19980804
AI US 1996-644931 19960513 (8) <--
RLI Continuation of Ser. No. US 1994-218875, filed on 25 Mar 1994, now

abandoned which is a continuation of Ser. No. US 1991-803634, filed on 6
Dec 1991, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Elliott, George C.; Assistant Examiner: Railey, II, Johnny F.
LREP Barnhard, Elizabeth M., Lowney, Karen A.
CLMN Number of Claims: 26
ECL Exemplary Claim: 1,7
DRWN 16 Drawing Figure(s); 10 Drawing Page(s)
LN.CNT 1478
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5789188 19980804 <--
DETD . . . of the CI gene that causes the Ind-phenotype (13), resulting in
a failure of .lambda. to be induced by the **SOS** system. After the introduction of the ind mutation, the microorganism is suitably specific for tetracyclines.
DETD . . . liquid assay is capable of detecting all tetracyclines previously known to have antibacterial activity. These compounds include
tetracycline, chlortetracycline, minocycline, **doxycycline**, 6-dimethyl chlortetracycline, and 6-deoxy-6-dimethyl tetracycline. Anhydro derivatives of tetracycline can also be detected, consistent with previous results (11).

L32 ANSWER 4 OF 4 USPATFULL
AB A salt of sucrose-octa-O-sulfonic acid and a tetracycline useful in inhibiting protein synthesis of bacteria.
AN 96:65545 USPATFULL
TI Salts of tetracyclines
IN Koch, Torben, Copenhagen, Denmark
Dyrsting, Hjarne, Virum, Denmark
PA A/S Dumex (Dumex Ltd.), Copenhagen, Denmark (non-U.S. corporation)
PI US 5538954 19960723 <--
AI US 1994-265193 19940624 (8)
DT Utility
FS Granted
EXNAM Primary Examiner: Peselev, Elli
LREP Watov & Kipnes
CLMN Number of Claims: 15
ECL Exemplary Claim: 1,5,7
DRWN 4 Drawing Figure(s); 4 Drawing Page(s)
LN.CNT 586
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5538954 19960723 <--
SUMM The invention relates to new salts of tetracyclines, especially **doxycycline**, and a process for the preparation thereof. The invention also relates to novel pharmaceutical compositions containing the new salts and. . .
SUMM The new salts comprise sucrose-octa-O-sulphonic acid and a tetracycline antibiotic with **doxycycline** being preferred.
SUMM . . . more than 50 years, the tetracyclines have been used as antibiotics. An especially valuable member of the tetracycline family is
**doxycycline**. This broad-spectrum antibiotic was first synthesised in 1962 and marketed by Pfizer under the name Vibramycin.RTM..
SUMM **Doxycycline** is available in several different salts:

**Doxycycline** monohydrate, **doxycycline** hydrochloride (hyclate), **doxycycline** carrageenate, **doxycycline** calcium and **doxycycline** phosphate (fosfatex).

SUMM **Doxycycline** shares its mode of action with other tetracyclines: Inhibition of bacterial protein synthesis. The inhibition is established through inhibition of. . . to 70S ribosomes but also to 30S ribosomes. The inhibition only leads to a bacteriostatic effect of the tetracyclines including **doxycycline**. Tetracyclines are active against a broad range of both gram positive and gram negative bacteria, aerobes as well as anaerobes. In all cases examined, **doxycycline** was found as effective as tetracycline and for several bacteria even more effective than tetracycline (Cunha 1982). Bacterial resistance to. . .

SUMM Most tetracyclines are incompletely absorbed and their absorption is dependent on the concomitant food intake. Absorption of **doxycycline** is almost complete (73-95%) and independent of food intake (Saivin, 1988).

SUMM The pharmacokinetic parameters of the different salts (hyclate, monohydrate, carrageenate) of **doxycycline** do not significantly differ under standard conditions (Saivin 1988, Grahnen 1991) and several comparative studies are found in the literature.

SUMM **Doxycycline** undergoes enterohepatic recycling-as first suggested by Gibaldi 1967, and later confirmed in pharmacokinetic profiles obtained by Malmborg 1984 and Nguyen. . . secondary peak in serum concentration due to reabsorption occurs around 10 to 12 hours after administration. Not all reports on **doxycycline** pharmacokinetics note the secondary peak, this can either be due to the fact that few samples are collected around the. . .

SUMM The relative long half life of **doxycycline** in combination with enterohepatic recycling leads to accumulation after multiple dosing of **doxycycline**. The terminal half life is up to 22 hours and therefore once a day dosage of **doxycycline** is possible (Schach von Wittenau 1974).

SUMM Two factors have been reported which influence the pharmacokinetics of **doxycycline**. The pH in the stomach (Grahn en 1991) and concomitant administration of oral antacids (Nguyen 1989).

SUMM An increased pH of the stomach (Bogardus 1979b) decreases the bioavailability of **doxycycline** monohydrate whereas **doxycycline** hyclate and **doxycycline** carrageenate dissociation and absorption are independent of pH.

SUMM The increased pH in the stomach after omeprazole administration is expected to slow down the dissolution of **doxycycline** monohydrate and thereby decrease its absorption.

SUMM The very long terminal half life of **doxycycline** is nicely demonstrated in the study of Nguyen 1989 where the 36 and 48 hours values has been performed in contrast to many other pharmacokinetic studies of **doxycycline**.

SUMM **Doxycycline** is lipophilic and is widely distributed in the tissues. High concentrations are found in renal tissue and gallbladder/bile. Therapeutic and. . . of ampicillin are-found in sinus secretions, palatine tonsils, nasal polyps and lung tissue (Cunha 1982, Saivin 1988). The Use of **doxycycline** in upper respiratory tract infections is therefore rational.

SUMM **Doxycycline** is not metabolised in humans (Saivin 1988). It is mainly excreted in faeces and approximately 20% can be recovered in urine. The **doxycycline** excreted in faeces is probably bound in a way that makes it inactive, as the intestinal flora is not affected by

**doxycycline** treatment (Cunha 1982).

SUMM **Doxycycline** is generally reported to be well tolerated (Cunha 1982).

SUMM **Doxycycline** was first introduced into clinical practice in 1968 as the HCl salt, called **doxycycline** hyclate. This salt was formulated in tablets or capsules. However, it was soon shown that these formulations had serious side effects. In a study of adverse drug reactions from antibiotics, 35/113 (31%) of patients treated with **doxycycline** hyclate after questioning reported nausea and vomiting while 24/373 (6.4%) spontaneously reported nausea and vomiting.

These frequencies where 3-fold higher. . .

SUMM Another side effect of **doxycycline** hyclate is esophageal ulceration, if the capsules for some reason do not reach the stomach but

remain in the oesophagus.

SUMM A solution to these problems has been attempted by the introduction of **doxycycline** hydrate (base). This new formulation has eliminated the above mentioned side effects, but it soon became apparent that the bioavailability. . .

SUMM This can be explained by the lack of acid production in the stomach being the cause of reduced dissolution of **doxycycline** hydrate.

SUMM . . . pH caused by either achlorhydria or due to the intake of antacids, H2-blockers, omeprazazole or the like, antibiotic treatment with **doxycycline** hydrate gives an unacceptable low bioavailability.

SUMM One solution to this problem has recently been suggested by the introduction of **doxycycline** carrageenate, which has a satisfactory bioavailability in subjects with elevated gastric pH. In subjects with normal pH conditions in the stomach, the use of **doxycycline** carrageenate has no advantages due to the spontaneous cleavage of **doxycycline** carrageenate into **doxycycline** H and carrageenate ion.

SUMM A study of cats (EP 091 409) showed that **doxycycline** carrageenate does not result in oesophagus ulcerations. No human safety data has been found on **doxycycline** carrageenate. To the best of our knowledge, no or very few clinical studies have been performed with **doxycycline** carrageenate and therefore a specific side effect profile of this **doxycycline** salt is not available.

SUMM By using different pharmaceutical preparations of **doxycycline**, attempts have been made to achieve a controlled release effect.

SUMM One solution to the aforementioned problems is the use of film coated tablets. A formulation with **doxycycline** hyclate was developed with less tendency to disintegration in the oesophagus (Delphre 1989). An enteric coated pellet formulation of **doxycycline** (Doryx.RTM., Doxylets.RTM.) has been developed to prevent the total dose

of **doxycycline** hyclate dissolving in a small area of the stomach. Such formulations have been shown to have a reduced (approximately 50%. . . Story 1991) and an unchanged bioavailability (Williams 1990). A pellet formulation does not have an automatically unchanged bioavailability. In a **doxycycline** pellet formulation developed at the University of Nanking, China it was found that 200 mg of the pellet formulation were bioequvivalent to 100 mg of the standard **doxycycline** hyclate formulation (Qiu 1986).

SUMM Therefore, a need exists for a **doxycycline** formulation with controlled release properties.

SUMM . . . belong to a group of antibiotics which are manufactured by fermentation of various Streptomyces species. The most widely used are **doxycycline**, oxytetracycline, chlorotetracyclines and

tetracycline. A number of semisynthetic tetracycline are known, for instance methacycline and minocycline. The most widespread of these semi-synthetic tetracyclines is .alpha.-deoxy-5-hydroxy-tetracycline ( **doxycycline**), which is manufactured by a 3-step synthesis with oxytetracycline as the starting material as described in U.S. Pat. No. 3,200,149. . .

SUMM U.S. Pat. No. 3,927,094 to Villax discloses the manufacture of alkali metal polymetaphosphate complexes of **doxycycline**; This salt is characterized by its high solubility in water.

SUMM In GB 2.088.864 to Villax, **doxycycline** mono-sodium-tetraphosphate is disclosed, which is also very water-soluble and has improved stability.

SUMM The sulfosalicylate of **doxycycline** is known from GB 1,305,860 to Alfa Farmaceutici. This salt is sparingly soluble in water and is used in the **doxycycline** manufacturing process. The sulfo-salicylic acid salt has no clinical use, as sulfosalicylic acid is not accepted for medicinal use.

SUMM In EP 91.409 Kabi Vitrum a complex between **doxycycline** and carrageenan is disclosed. Carrageenan is a sulphated polysaccharide with a molecular weight from 100,00 to 100,000. This complex is insoluble in water. By dissolution, it is shown that the **doxycycline** hydrocarrageenate complex releases the active substance at the same rate-as **doxycycline** hyclate in the gastric juice.

SUMM Useful antibiotics of this group consist of tetracycline itself, **doxycycline**, oxytetracycline, chlorotetracycline, metacycline and minocycline. Especially valuable is **doxycycline**, which is a 6-deoxy derivative of oxytetracycline with the following chemical name and formula: ##STR2## 4-dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide monohydrate.

SUMM . . . a tetracyclines antibiotic in water with an aqueous solution of sucrose-octa-O-sulphonic acid. Particularly preferred is a method where e.g. the **doxycycline** salt of sucrose-octa-O-sulphonic acid which has the general formula:

SUMM [sucrose-octa-O-sulphate.sup.8- ]-[**doxycycline** H.sup.+ ].sub.8, x H.sub.2 O]

SUMM hereinafter referred to as **doxycycline** sucrose octasulphate, is produced by treatment of a solution of **doxycycline** in hydrochloric acid with an aqueous solution of sucrose-octa-O-sulphonic acid sodium salt.

SUMM **Doxycycline** sucrose octasulphate contains about 70% (10% water). **doxycycline** and this makes the salt well suited for preparation tablets of a suitable size.

SUMM . . . the individual needs of each patient and-administration's preferences. The dose will be on the same level as normally used for **doxycycline**, which generally ranges from 100-400 mg/day.

SUMM The dissolution properties of the **doxycycline** sucrose octasulphate according to the invention can easily be demonstrated by the method described in example 6. It is surprising that the new salts have the same dissolution properties as known formulations, in which **doxycycline** is bound to polymers with high molecular weight, as for instance carrageen.

SUMM . . . also be used locally on the skin, or mucous membranes formulated as creams, lotions, ointments or gels. As an example, **doxycycline** sucrose octasulphate is well suited for insertion

into or around the periodontal pocket of an individual suffering from perodontitis. In. . .

SUMM The invention further relates to the use of a salt of sucrose-octa-O-sulfonic acid and a tetracycline, preferably **doxycycline**, for the preparation of a medicament.

DRWD FIG. 1 shows a DSC scan for **doxycycline** sucrose octasulphate showing a characteristic endothermic peak at about 130.degree. C.;

DRWD FIG. 2 shows the infrared spectrum of **doxycycline** sucrose octasulphate;

DRWD FIG. 3 shows the NMR spectrum of **doxycycline** sucrose octasulphate; and

DRWD . . . of the percentage release of antibiotic against time for three 100 mg tablets, the first containing vibramycin, the second containing **doxycycline** sucrose octasulphate salt and Tween and the third containing **doxycycline** sucrose octasulphate salt without Tween.

DETD 18.5 g (40 mmol) **doxycycline** monohydrate is dissolved in 400 ml 0.1M HCl and by addition of 6.5 g (5 mmol), sucrose-octa-O-sulphonic acid-Na.sub.8, 8 aq., dissolved in 300 ml water, precipitation of **doxycycline** sucrose octasulphate takes place. The reaction mixture is stirred for -60 min. at 25.degree. C., filtered, washed with 3.times.50 water. . .

DETD DSC: (FIG. 1) **Doxycycline** sucrose octasulphate shows a characteristic endoterm peak at about 130.degree. C. The substance does not have a welldefined melting point,. . .

DETD Stoichiometric proportions: In the batches produced, the content of water was found to be about 10%. The content of **doxycycline** was found to be about 77%, calculated with reference to the dried substance. This content of **doxycycline** indicates that 8moles of **doxycycline** complexes with 1 mole of sucrose-octa-O-sulphonic acid.

DETD The IR and NMR spectra for **doxycycline** sucrose octasulphate are shown in FIGS. 2 and 3.

DETD Signal originating from **doxycycline**;

DETD 20.5 g **doxycycline** hyclate (40 mmol) is dissolved in 400 ml water and with vigorous stirring, 100 ml of the acid solution of. . .

DETD 18.5 g (40 mmol) **doxycycline** monohydrate is dissolved in 400 ml 0.1M HCl and by titration with 100 ml 0.05M (5 mmol) sucrose-octa-O-sulphonic acid precipitation of **doxycycline** sucrose octasulphate takes place. The reaction mixture is stirred for -60 min. at 25C, filtered, washed with 3.times.50 ml water. . .

DETD . . . of 6.5 g (5 mmol) sucrose-octa-O-sulphonic acid Na.sub.8, 8 aq.

dissolved in 300 ml water, with 18.5 g (40 mmol) **doxycycline** monohydrate dissolved in 400 ml 0.1M HCl, precipitation of **doxycycline** sucrose octasulphate takes place. The reaction mixture is stirred for -60 min. at 25.degree. C., filtered, washed with 3.times.50 ml. . .

DETD Dissolution of **doxycycline** sucrose octasulphate:

DETD . . . used in accordance with USP XXII, p. 1579, (apparatus II), with

900 ml 0.1N HCl. One tablet containing 150, mg **doxycycline** sucrose octasulphate (equal to 105 mg **doxycycline**) is placed in the dissolution apparatus. Samples are taken after 5, 10, 20, 30, and

60 minutes and diluted.

DETD The results are compared to samples of Vibramycin.RTM. from Pfizer, which contains **doxycycline** carrageenate.

DETD TABLE I

Comparison of Vibramycin and **Doxycycline SOS** tablets 100 mg

| Time (minutes) | Vibramycin | **Doxycycline-SOS** with Tween | **Doxycycline-SOS** without Tween |
|---|---|---|---|
| 0 | 0 | 0 | 0 |
| 5 | 37.45 | 45.89 | 42.02 |
| 10 | 56.06 | 56.12 | 57.22 |
| 20 | 76.75 | 73.31 | 79.54 |
| 30 | 88.08 | 81.42 | 91.06 |
| 60 | 98.67. . . | | |


DETD Bogardus JB, Blackwood RK (1979) Dissolution rates of **doxycycline** free base and hydrochloride salts. J Pharm Sciences 68, 1183-1184.

DETD Cunha BA, Sibley CM, Ristuccia AM (1982) **Doxycycline**. Therapeutic drug Monitoring 4, 115-135.

DETD Delphre G, Kadish U, Stahl B (1989) Induction of esophageal injuries by **doxycycline** and other pills. Digestive diseases and Sciences 34, 797-800.

DETD Gibaldi M (1967) Pharmacokinetics of absorption and elimination of **doxycycline** in man. Chemoterapia 12, 265-271.

DETD Grahnen A, Lonnebo A, Eckernas S-A (1991) Effect of increasing gastric pH on the relative bioavailability of **doxycycline** carrageenate tablets 100 mg (kabi Pharmacia) in comparison. Internal study report, PCB, Sweden.

DETD Khouzam S, Yazbeck D (1987) Etude comparative de la tolerance gastrique de 1' hyclate de **doxycycline** apres administration orales uniques croisees de deux formulations. Acta Therapeutica 3, 309-315.

DETD Maltaborg A-S (1984) Bioavalability of **Doxycycline** Monohydrate. A comparison with equivalent doses of **doxycycline** hydrochloride. Chemotherapy 30, 76-80.

DETD Nguyen VX, Nix DE, Gillikin S, Schentag JJ (1989) Effect of oral antacid administration on the pharmacokinetics of intraveneous **doxycycline**. Antimicrob. Agents Chemother. 33, 434-436.

DETD Qiu Y-H, Tu X-D, Mao F-F (1986) Development and pharmacokinetic study of sustained release **doxycycline** hydrochloride pellets. Acta Pharmaceutic Sinica 21, 370-376.

DETD Saivin S, Houin G (1988) Clinical pharmakokinetics of **doxycycline** and minocycline. Clinical Pharmakokinetics 15, 355-366.

DETD Schach von Wittenau M (1974) Pharmacokinetics of **Doxycycline**. Opuscula Medica 53 (Suppl. 23) 5-10.

DETD Story MJ, McCloud PI, Boehm G (1991) **Doxycycline** tolerance study. Incidence of nausea after **doxycycline** administration to healthy volunteers: A comparison of 2 formulations (Doryx' vs Vibramycin'). Eur J Clin Pharmacol 40, 419-421.

DETD Williams DB, O'Reilly WJ, Boehm G, Story MJ (1990) Absorption of **doxycycline** from a controlled release pellet formulation: The influence of food on bioavailability. Biopharmaceutics & Drug disposition 11, 93-105.


CLM What is claimed is:

3. A salt according to claim 2, wherein "TC" is selected from the group consisting of **doxycycline**, tetracycline, oxytetracycline, chlorotetracycline, metacycline and minocycline.

4. A salt according to claim 3, wherein "TC" is **doxycycline**.

9. The method of claim 7 wherein a tetracycline is selected from the group consisting of **doxycycline**, tetracycline, oxytetracycline, chlorotetracycline, metacycline and minocycline.

10. The method of claim 9 wherein a tetracycline is **doxycycline**.

12. The pharmaceutical composition of claim 5 wherein a tetracycline is selected from the group consisting of **doxycycline**, tetracycline, oxytetracycline, chlorotetracycline, metacycline and minocycline.

13. The pharmaceutical composition of claim 12 wherein a tetracycline is **doxycycline**.

```
=> s matrix metalloproteinase inhibitor or MMP inhibitor or matrix
metalloproteinase blocker or MMP blocker
L33       4919 MATRIX METALLOPROTEINASE INHIBITOR OR MMP INHIBITOR OR MATRIX
               METALLOPROTEINASE BLOCKER OR MMP BLOCKER

=> s sinusoidal obstruction syndrome or SOS or hepatic venoocclusive disease
   3 FILES SEARCHED...
L34      16748 SINUSOIDAL OBSTRUCTION SYNDROME OR SOS OR HEPATIC
VENOOCCLUSIVE
               DISEASE

=> s l33 and l34
L35          0 L33 AND L34

=> s s liver or hepati?
L36     813572 S LIVER OR HEPATI?

=> s l33 and l36
L37        192 L33 AND L36

=> s l37 and doxycycline
L38         11 L37 AND DOXYCYCLINE

=>  s l38 and py<2001
   2 FILES SEARCHED...
L39          2 L38 AND PY<2001

=> d l39 1-2

L39  ANSWER 1 OF 2  USPATFULL
AN     1999:72602  USPATFULL
TI     Conjugates of dithiocarbamates with pharmacologically active agents and
       uses therefore
IN     Lai, Ching-San, Encinitas, CA, United States
PA     Medinox, Inc., San Diego, CA, United States (U.S. corporation)
PI     US 5916910              19990629                                  <--
AI     US 1997-869158          19970604 (8)
DT     Utility
FS     Granted
LN.CNT 1842
INCL   INCLM: 514/423.000
```

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       INCLS: 514/514.000; 548/564.000; 548/573.000; 558/235.000
NCL    NCLM:  514/423.000
       NCLS:  514/514.000; 548/564.000; 548/573.000; 558/235.000
IC     [6]
       ICM: C07D207-04
       ICS: C07D207-30; A61K031-27; A61K031-40
EXF    514/514; 514/423; 548/565; 548/573; 558/235
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L39  ANSWER 2 OF 2  USPATFULL
AN     1998:98932  USPATFULL
TI     DHA-pharmaceutical agent conjugates of taxanes
IN     Shashoua, Victor E., Brookline, MA, United States
       Swindell, Charles S., Merion, PA, United States
       Webb, Nigel L., Bryn Mawr, PA, United States
       Bradley, Matthews O., Laytonsville, MD, United States
PA     Neuromedica, Inc., Conshohocken, PA, United States (U.S. corporation)
PI     US 5795909              19980818                                <--
AI     US 1996-651312          19960522 (8)
DT     Utility
FS     Granted
LN.CNT 2451
INCL   INCLM: 514/449.000
       INCLS: 514/549.000
NCL    NCLM:  514/449.000
       NCLS:  514/549.000
IC     [6]
       ICM: A61K031-335
       ICS: A61K031-22
EXF    514/449; 514/549
CAS INDEXING IS AVAILABLE FOR THIS PATENT.


=> d 1-2 ab bib

L39  ANSWER 1 OF 2  USPATFULL
AB     In accordance with the present invention, there are provided conjugates
       of nitric oxide scavengers (e.g., dithiocarbamates, or "DC") and
       pharmacologically active agents (e.g., NSAIDs). Invention conjugates
       provide a new class of pharmacologically active agents (e.g.,
       anti-inflammatory agents) which cause a much lower incidence of
       side-effects due to the protective effects imparted by modifying the
       pharmacologically active agents as described herein. In addition,
       invention conjugates are more effective than unmodified
       pharmacologically active agents because cells and tissues contacted by
       the pharmacologically active agent(s) are protected from the
potentially
       damaging effects of nitric oxide overproduction induced thereby as a
       result of the co-production of nitric oxide scavenger (e.g.,
       dithiocarbamate), in addition to free pharmacologically active agent,
       when invention conjugate is cleaved.
AN     1999:72602  USPATFULL
TI     Conjugates of dithiocarbamates with pharmacologically active agents and
       uses therefore
IN     Lai, Ching-San, Encinitas, CA, United States
PA     Medinox, Inc., San Diego, CA, United States (U.S. corporation)
PI     US 5916910              19990629                                <--
AI     US 1997-869158          19970604 (8)
DT     Utility
FS     Granted
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EXNAM Primary Examiner: Davis, Zinna Northington
LREP Reiter, Esq., Stephen E.Gray, Cary, Ware & Freidenrich
CLMN Number of Claims: 27
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1842
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L39 ANSWER 2 OF 2 USPATFULL
AB The invention provides conjugates of cis-docosahexaenoic acid and taxanes useful in treating cell proliferative disorders. Conjugates of paclitaxel and docetaxel are preferred.
AN 1998:98932 USPATFULL
TI DHA-pharmaceutical agent conjugates of taxanes
IN Shashoua, Victor E., Brookline, MA, United States
Swindell, Charles S., Merion, PA, United States
Webb, Nigel L., Bryn Mawr, PA, United States
Bradley, Matthews O., Laytonsville, MD, United States
PA Neuromedica, Inc., Conshohocken, PA, United States (U.S. corporation)
PI US 5795909 19980818 <--
AI US 1996-651312 19960522 (8)
DT Utility
FS Granted
EXNAM Primary Examiner: Jarvis, William R. A.
LREP Wolf, Greenfield & Sacks, P.C.
CLMN Number of Claims: 12
ECL Exemplary Claim: 1
DRWN 27 Drawing Figure(s); 14 Drawing Page(s)
LN.CNT 2451
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d 1-2 kwic

L39 ANSWER 1 OF 2 USPATFULL
PI US 5916910 19990629 <--
SUMM . . . motility disorders, obesity, hyperphagia, solid tumors (e.g., neuroblastoma), malaria, hematologic cancers, myelofibrosis, lung injury, graft-versus-host disease, head injury, CNS trauma, **hepatitis**, renal failure, liver disease (e.g., chronic **hepatitis** C), drug-induced lung injury (e.g., paraquat), myasthenia gravis (MG), ophthalmic diseases, post-angioplasty, restenosis, angina, coronary artery disease, and the like.
SUMM . . . erythromycins (e.g., erythromycin ethylsuccinate, erythromycin, erythromycin estolate, erythromycin lactobionate, erythromycin siearate, erythromycin ethylsuccinate, and the like), tetracyclines (e.g., tetracycline hydrochloride, **doxycycline** hyclate, minocycline hydrochloride, and the like), and the like);
SUMM . . . antibody therapeutics, murine MAb (e.g., anti-SLE vaccine, and MAb 3E10), primatized anti-CD4 antibodies (e.g., CE9.1), protease inhibitors (e.g., matrix metalloprotease (**MMP**) **inhibitors**, and stromelysin), protein synthesis antagonists (e.g., anti-CD6-bR, anti-T12-bR, and oncolysin CD6), purine nucleoside phosphorylase inhibitors (e.g., BCX-25, and BCX-14), selectin. . .
SUMM . . . cimetidine, ciprofloxacin, cisapride, clarithromycin, clavulanate, clonazepam, clotrimazole, codeine, conjugated estrogens, cyclobenzaprine, desogestrel, dexrazoxane, diazepam, dicyclomine HCI, digoxin, diltiazem, dirithromycin, doxazosin, **doxycycline**,

enalapril, erythromycin, erythromycin base, erythromycin stearate, estradiol, ethinyl estradiol, ethynodiol diacetate, etodolac, famotidine, fluconazole, fluoxetine, fluvastatin, furosemide, gemfibrozil, glipizide, glyburide,. . .

L39 ANSWER 2 OF 2 USPATFULL
PI US 5795909 19980818 <--
DETD . . . Coumermycin Sodium; Cyclacillin; Cycloserine; Dalfopristin; Dapsone; Daptomycin; Demeclocycline; Demeclocycline Hydrochloride; Demecycline; Denofungin; Diaveridine; Dicloxacillin; Dicloxacillin Sodium; Dihydrostreptomycin Sulfate; Dipyrithione; Dirithromycin; **Doxycycline**; **Doxycycline** Calcium; **Doxycycline** Fosfatex; **Doxycycline** Hyclate; Droxacin Sodium; Enoxacin; Epicillin; Epitetracycline Hydrochloride; Erythromycin; Erythromycin Acistrate; Erythromycin Estolate; Erythromycin Ethylsuccinate; Erythromycin Gluceptate; Erythromycin Lactobionate; Erythromycin Propionate;. . .
DETD . . . lombricine; lometrexol; lonidamine; losoxantrone; lovastatin; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocol; maspin; matrilysin inhibitors; **matrix metalloproteinase inhibitors**; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin. . .
DETD . . . (Micrurus Fulvius); Antivenin (Crotalidae) Polyvalent; BCG Vaccine; Botulism Antitoxin; Cholera Vaccine; Diphtheria Antitoxin; Diphtheria Toxoid; Diphtheria Toxoid Adsorbed; Globulin, Immune; **Hepatitis** B Immune Globulin; **Hepatitis** B Virus Vaccine Inactivated; Influenza Virus Vaccine; Measles Virus Vaccine Live; Meningococcal Polysaccharide Vaccine Group A; Meningococcal Polysaccharide Vaccine Group. . .

=> s deleve,l?/au
L40 101 DELEVE,L?/AU

=> s wang,x?/au
L41 38821 WANG,X?/AU

=> s l40 and ;41
MISSING TERM AFTER L40 AND
COMMAND STACK INTERRUPTED. ENTER "DISPLAY HISTORY"
TO SEE WHICH COMMANDS WERE EXECUTED.

Operators must be followed by a search term, L-number, or query name.

=> s l40 and l41
L42 30 L40 AND L41

=> s Tsai,j?/au
L43 3856 TSAI,J?/AU

=> s l42 and l43
L44 2 L42 AND L43

=> d l44 1-2

L44 ANSWER 1 OF 2 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2002:175859 BIOSIS

DN PREV200200175859
TI Prevention of hepatic venoocclusive disease in the rat by inhibition of matrix metalloproteinases.
AU **DeLeve, Laurie D. (1); Wang, Xiangdong (1); Tsai, Jeffrey (1)**; Kanel, Gary (1); Tokes, Zoltan (1)
CS (1) USC Keck Sch of Medicine, Los Angeles, CA USA
SO Gastroenterology, (April, 2001) Vol. 120, No. 5 Supplement 1, pp. A.54. http://www.gastrojournal.org/. print.
Meeting Info.: 102nd Annual Meeting of the American Gastroenterological Association and Digestive Disease Week Atlanta, Georgia, USA May 20-23, 2001
ISSN: 0016-5085.
DT Conference
LA English

L44 ANSWER 2 OF 2 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2001:248876 BIOSIS
DN PREV200100248876
TI Toxin induced matrix metalloproteinases may damage hepatic sinusoidal integrity.
AU **DeLeve, Laurie D. (1); Tsai, Jeffrey**; Wang, Peixin; **Wang, Xiangdong (1)**; Park, Ji Min; Tokes, Zoltan A.
CS (1) Div. of Gastrointestinal and Liver Diseases, Dept. of Pathology, University of Southern California, 1303 N. Mission Road, Los Angeles, CA, 90033 USA
SO FASEB Journal, (March 7, 2001) Vol. 15, No. 4, pp. A26. print.
Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA March 31-April 04, 2001
ISSN: 0892-6638.
DT Conference
LA English
SL English

=> d kwic 1-2

L44 ANSWER 1 OF 2 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AU **DeLeve, Laurie D. (1); Wang, Xiangdong (1); Tsai, Jeffrey (1)**; Kanel, Gary (1); Tokes, Zoltan (1)

L44 ANSWER 2 OF 2 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AU **DeLeve, Laurie D. (1); Tsai, Jeffrey**; Wang, Peixin; **Wang, Xiangdong (1)**; Park, Ji Min; Tokes, Zoltan A.

=> d ab 1-2

L44 ANSWER 1 OF 2 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

L44 ANSWER 2 OF 2 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AB Monocrotaline (MCT), a pyrrolizidine alkaloid, is a prototypical toxin that causes hepatic venoocclusive disease (VOD). An important early event in monocrotaline-induced VOD is the rounding up of sinusoidal endothelial cells with subsequent dissection of the sinusoidal lining, which embolizes into the sinusoids. These events precede the clinical manifestations of VOD which occur 72 hrs after MCT treatment. The loss of sinusoidal integrity suggests a possible role for matrix metalloproteinases (MMPs). This study examines whether MMPs contribute to sinusoidal damage by MCT.

Sprague-Dawley rats, 270 g, were treated with 160mg/kg MCT i.g. on day 0. For MMP inhibition studies, rats were given 15mg/kg doxycycline (DOX) b.i.d. starting 48 hrs prior to the MCT treatment. Measurements of MMP mRNA and activity were done 48 hrs after MCT treatment (day 2). MMP mRNA synthesis was assessed by RT-PCR and Taqman assays. MMP activity in liver was measured by zymography. Ten to 17-fold increase in MMP-9 activity was detected by zymography on day 2 compared to control liver, whereas increase in MMP-2 were less than two fold. MMP-9 mRNA levels detected by RT-PCR and Taqman were 4 to 24 folds higher on day 2 than in controls. DOX treatment prevented histologic evidence of VOD on days 4 and 6. DOX analogues that do not inhibit MMPs had little or no effect on VOD. DOX did not alter total MMP-9 and MMP-2 levels determined by zymography indicating that the drug did not inhibit MMP synthesis. Note that zymography conditions dissociate enzyme-inhibitor complexes and cannot detect the effect of inhibitors on enzymes. These data suggest that in MCT-induced VOD, increased MMP-9 activity may contribute to the destruction of hepatic sinusoids.

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